Role of therapeutic hypothermia on neurological outcome in post cardiac arrest patients

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(MAY, 2021)

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I declare that the thesis entitled "**ROLE OF THERAPEUTIC HYPOTHERMIA ON NEUROLOGICAL OUTCOME IN POST CARDIAC ARREST PATIENTS**" has been prepared by me under the guidance of **DR. RAJINDER BANSAL**, Professor, Department of Neurology, Dayanand Medical College and Hospital, Ludhiana. No part of this thesis has formed the basis for the award of any degree previously.

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Dedicated

to

my Family,
Teachers

&

Friends

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Dr. Nitika Mahajan

ABBREVATIONS

TH	Therapeutic hypothermia
TIMH	Therapeutic induced moderate hypothermia
AHA	American heart association
SSEP	Somato sensory evoked potential
AAN	American academy of neurology
VF	Ventricular fibrillation
ILCOR	International Liaison committee on resuscitation
ALS	Advanced life support
GCS	Galssgow coma scale
EEG	Electroencephalogram
K+	Potassium
Mg++	Magnesium
Ca++	Calcium
CPR	Cardiopulmonary resuscitation
ROSC	Return of spontaneous circulation
DAMA	Discharge against medical advise
HACA	Hypothermia after cardiac arrest
ICU	Intensive care unit
mRS	Modified Rankin scale
FOUR score	Full outline of unresponsiveness
CPC	Cerebral performance category scale

KEY TO MASTER CHART

1.	S.no	-	Serial Number
2.	M	-	Male
3.	F	-	Female
4.	I	-	improved
6	w	-	worse
7	n	-	no change
8	Y	-	yes

ABSTRACT

Introduction:.Therapeutic hypothermia is defined as an intentional reduction of a patients' core temperature to 32°C–35°C.Since there are well established guidelines for the potential benefits of hypothermia on the neurological recovery of post cardiac arrest patients, we would further like to look at the feasibility, safety and effectiveness of hypothermia in our hospital setting.

Aim of Study: To study the effect of therapeutic hypothermia on neurological outcome in post cardiac arrest patients

Materials & methods: We conducted a prospective observational study on a total of 20 patients. Those patients who were cardiac arrest survivors and remained comatose post CPR were enrolled in our study. Hypothermia was created using a special blanket/ mattress. The provision of therapeutic hypothermia to survivors of cardiac arrest consisted of three phases: Induction, Maintenance and Rewarming.

Results: The outcomes of the patients who underwent hypothermia post cardiopulmonary resuscitation were as follows: 40% of the patients got discharged, 40% died while the rest 20% went discharge against medical advice. There was a trend towards improvement of FOUR score from the baseline after hypothermia although the value is non significant (p value=0.086). The mean mRS at baseline and outcome was 5±0 and 4.9±1.07 while the mean CPC values at baseline and outcome was 4.05±0.22 and 3.95±1.1 respectively. We compared the survival rates and neurological outcomes in group 1(out of hospital) and 2(in hospital) cardiac arrest patients. The number of patients who survived was higher in group 1(55.6%) as compared to group 2(27.3%).. There was a trend towards improvement of FOUR score, CPC and mRS scale in patients of group 1 vs group 2.

Conclusion: Therapeutic hypothermia helps improve the neurological recovery and survivor in post cardiac arrest survivors.

Keywords: Therapeautic hypothermia, post CPR, FOUR score, mRS , CPC scale

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INTRODUCTION

Therapeutic hypothermia is defined as an intentional reduction of a patients' core temperature to 32°C–35°C. This is being used with increasing frequency as a method to prevent various types of neurologic injury.[1] Hence, the issue of temperature control and temperature manipulation is gaining importance in neurocritical care. According to the most recent guidelines from the American Heart Association and the European Resuscitation Council it is recommended to induce hypothermia for selected patients who remain comatose following a witnessed cardiac arrest.[2] Therapeutic hypothermia is also used therapeutically in the treatment of severe traumatic brain injury, stroke, hepatic failure, spinal cord injury, myocardial infarction, and numerous others.The evidence for these potential indications has been elucidated in various reviews.[1,3,4]Although the clinical trials of TH for head trauma and stroke have so far failed to confirm any benefit in human beings despite a vast preclinical literature. Therefore, it is now critical to understand the fundamental explanation for the success of TH in some, but not all, clinical trials. However, the role of therapeutic hypothermia has been proven in patients of post cardiac arrest and in neonatal hypoxic ischemic encephalopathy.

Proposed terms and definitions surrounding therapeutic hypothermia[3]

Therapeutic temperature management definitions

Hypothermia- Core temperature 36.0°C regardless of the cause

Induced hypothermia - An intentional reduction of a patients' core temperature below 36.0°C.

Therapeutic hypothermia- Controlled induced hypothermia: i.e., inducedhypothermia with the potentially deleterious effects, such as shivering, being controlled or suppressed.

Temperature range definitions

Mild therapeutic hypothermia - An intentional and controlled reduction of a patients' core temperature to 34.0°C–35.9°C

Moderate therapeutic hypothermia - An intentional and controlled reduction of a patients' core temperature to 32.0°C–33.9°C
Deep therapeutic hypothermia - An intentional and controlled reduction of a patients' core temperature to 30.0°C.

Since there are well established guidelines for the potential benefits of hypothermia on the neurological recovery of post cardiac arrest patients, we would further like to look at the feasibility, safety and effectiveness of hypothermia in our hospital setting.

AIMS AND OBJECTIVES

- To study the effect of therapeutic hypothermia on neurological outcome in post cardiac arrest patients.

REVIEW OF LITERATURE

Cardiac arrest is often associated with widespread cerebral ischemia which frequently leads to severe neurologic impairment. Our body undergoes a lot of physiological changes post cardiac arrest. There are several mechanisms proposed for neuronal injury post cardiac arrest. Studies have mentioned that the lack of cerebral oxygenation during cardiac arrest results in loss of ATP production and dysfunction of membrane ATP–dependent Na-K pumps. There is subsequent loss of cellular integrity which triggers the release of glutamate, which causes excitotoxicinjury[5] mediated through N-methyl-D-aspartate (NMDA) receptors.[6] Other neurotransmitters which dampen the excitotoxicity of glutamate, like glycine and gaminobutyric acid (GABA), are decreased concomitantly.[7]The activation of NMDA receptors by glutamate results in influx of calcium into the intracellular space which activates a series of second messengers. This further leads to amplification of cell injury by increasing calcium permeability and glutamate release.[8] During re-perfusion, excitotoxicity is further increased by providing oxygen as a substrate for several enzymatic oxidation reactions that leads to production of free radicals in the setting of mitochondrial dysfunction.[9] These reactive oxygen species cause injury through DNA fragmentation, lipid peroxidation, and protein oxidation thus leading to cell death.[6] Several reviews provide a detailed description of the mechanisms of neuronal injury that are related to global ischemia.[10-14]Although the mechanism underlying the neuroprotective effect of hypothermia is not fully understood, numeroushypotheses have been suggested.[15] Hypothermia affects multiple points of the injury cascade thereby contributing significantly to its successful intervention. The effects of hypothermia include decreasing the initial rate of ATP depletion,[16,17] altering gene expression and protein synthesis,[18,19] decreasing inflammatory responses,[20]reducing excitotoxic neurotransmitter release,[21]altering intracellular messenger activity,[22]limiting breakdown of the blood-brain barrier,[23]reducing intracellular calcium, and changing glutamate receptor regulation.[24]

The neurologic injury postcardiac arrest results in a heterogeneous manner. The most vulnerable areas are projection neurons of the cerebral cortex, cerebellar Purkinje cells, and the CA-1 area of the hippocampus.[25]Other areas like basal ganglia and cerebellum, which account for movement disorders and incoordinationare also prone to ischemic injury.The subcortical areas of the brain such as the brainstem, thalamus, and hypothalamus are resistant to hypoxic injury as compared to the cortex.[26,27] In 2008 Hoesch and colleagues published a review on neuroanatomic and physiologic considerations of coma related to brain injury after cardiac arrest [28]. The brainstem can tolerate a much greater degree of cerebral ischemia which is manifested as a preservation of the cranial nerve and sensory motor reflexes.

However, it has been seen that temperature regulation post arrest plays an important role as a predictor of neurological recovery. It has been demonstrated that moderate hyperthermia markedly exacerbates the degree of resulting neural injury during or after a period of brain ischemia or trauma. The outcomes of focal and global cerebral ischemia are profoundly affected by alterations in body temperature in laboratory animals.[29,30] However, experimental mammalian models have proven that even mild hyperthermia of up to 2°C above normal significantly increases ischemic neuronal injury.[31] Terent and Andersson[32]observed that in patients with cerebrovascular ischemic attacks and stroke,fever (temperature ≥38°C) was significantly associated with poor prognosis. There are a few investigations[33,34] on the impact of the natural course of body temperature on the neurologic outcome after successful cardiopulmonary resuscitation. Zeiner A[35]et al observed that Patients with a higher lowest temperature within 4 hours (35.8°C [35.0°C-36.1°C] vs 35.2°C [34.5°C-35.7°C]; *P* = .002) and a lower highest temperature during the first 48 hours after return of spontaneous circulation (37.7°C [36.9°C-38.6°C] vs 38.3°C [37.8°C-38.9°C]; *P*<.001) showed a favourable neurologic recovery and thereby concluded that hyperthermia is a potential risk factor for poor functional neurologic recovery after cardiopulmonary resuscitation

Therapeutic hypothermia has been recommended for post cardiac arrest coma due to ventricular fibrillation. M. Holzer et al[36] studied whether mild systemic hypothermia increases the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation. They conducted a randomised study on 136 patients who had been successfully resuscitated after cardiac arrest. They thereby concluded that therapeutic mild hypothermia increased the rate of a favourable neurologic outcome and reduced mortality in patients who had received therapeutic hypothermia. There is paucity of studies which have evaluated whether therapeutic hypothermia could be effectively implemented in intensive care practice and whether it would improve the outcome of all comatose patients with cardiac arrest, including those with shock or with cardiac arrest due to nonventricular fibrillation rhythms. Mauro Oddo et al[37] conducted a Retrospective study on109 comatose patients with outof hospital cardiac arrest due to ventricular fibrillation and non-ventricular fibrillation rhythms (asystole/pulseless electrical activity). They found that therapeutic hypothermia had a major positive impact on the outcome of patients with cardiac arrest due to ventricular fibrillation as compared to patients who had arrest due to non-VF rhythms. Therapeutic hypothermia was of particular benefit in patients with short duration of cardiac arrest (<30 minutes). They concluded that therapeutic hypothermia for the treatment of post cardiac arrest coma can be successfully implemented in intensive care practice with a major benefit on patient outcome, which appeared to be related to the type and the duration of initial cardiac arrest. Therapeutic Hypothermia (TH) has been shown to improve neurological recovery and reduces mortality after global ischemia, such as in patients with cardiac arrest,[36,38,39] and also in infants with moderate or severe hypoxic-ischemic encephalopathy.[40]There are several hypothesis explained in literature about the rationale of hypothermia in post cardiac arrest patients. After restoration of blood flow, reperfusion injury occurs in the brain[41] and heart.[42] It includes release of proinflammatory mediators followed by anti-inflammatory cytokines. This in turn leads to poor capillary

perfusion, tissue ischemia, and microcirculatory dysfunction. The extent of reperfusion injury is associated with the duration of ischemia, and the adequacyof resuscitation. The long-term prognosis is directly related with the extent of reperfusion injury.Givingtherapeutic hypothermia during ischemia prolongs the tolerance of organs to ischemia. Hypothermia after reperfusion leads to decreased production of deleterious glutamate, inflammatory molecules,oxygen free radicals, cerebral oxygen demand, intracranial pressure, and hence the final extent of neurological injury.[21] It is an important question when to initiate hypothermia after cardiac arrest. Hypothermia started 4 to 8 hours after resuscitation, is associated with the improvement of neurological outcome compared with normothermia.[36,38] The application of ice packs for hypothermia induction is limited because of relatively slow induction times to temperatures <34°C compared with other methods.Initial clinical trials had focused on target core temperature of 32°C to 34°C, for an average of 12 to 24 hours.[36,38]However, there was criticism of the post cardiac arrest hypothermia trial because the average temperature in the normothermia control group remained >37°C, and some patients had even developed fever between 8 to 36 hours after return of spontaneous circulation.[36] It remains questionable whether the improved survival and neurological outcomes seen in the hypothermia study were partly because of the therapeutic effects of mild hypothermia or the avoidance of hyperthermia after the first 24 hours post OHCA. Thisbecomes relevant as the development of hyperthermia during the first 36 to 48 hours post cardiac arrest is associated with unfavourable outcomes in comatose patients.[35,43] The history of use of hypothermia dates back to 1940- 1950.The successful use of induced hypothermia post cardiac arrest in humans was first described in the late 1950s.[44-46]Therapeutic hypothermia was described as a therapy for acute brain injury in the 1940s by Fay.[47] In 1950, Bigelow and colleagues[48] had reported the use of hypothermia during cardiac surgery. In the 1980s, researchers of Pittsburgh[13,14]and Miami[15,49] dealt with induced hypothermia for brain injury in a more

systematic manner. Bernard and colleagues[50]performed a first human clinical study on induced hypothermia for survivors of out-of hospital cardiac arrest in 1997. In 1998, Yanagawa and colleagues[51] conducted a study of 13 post arrest survivors who were cooled upto a temperature of 33°C for 48 hours using the cooling blankets and convective heat loss through alcohol evaporation.After an out-of-hospital ventricular fibrillation (VF) arrest,mildtherapeutic(32–34°C for 12–24 hours has been shown to improve neurological outcome in comatose patients.[36,38] The International Liaison Committee on Resuscitation (ILCOR) has suggested that there may be a potential benefit for the use of hypothermia in the non VF rhythm cardiac arrest group of patients although the evidence base is less robust.[52]Both fixed dilated pupils and a Glasgow Coma Score (GCS) motor response of 1 were historically correlated with poor neurological prognosis in the immediate post-arrest phase[53] Myoclonic status in the immediate post-arrest phase is associated with a hopeless neurological prognosis.[53,54]In a recent small study of post-cardiac arrest patients treated with TH, a small number of patients with absent corneal or pupillary reflexes on day 3 or myoclonic status epilepsy regained awareness[55]In patients undergoing TH, a persistently low GCS of 4 or less on the fourth day after cessation of sedation suggests a poor neurological outcome with a specificity of 95%.[56]

Yannopoulos D et al[57]reported 4 comatose post cardiac arrest patients who were treated with mild hypothermia. All patients had a GCS between 3 and 6 and a FOUR Score between 1 and 5 on hospital admission. They implemented mild hypothermia (32°C–33°C) for 24 to 40 hours. They observed that all 4 patients had a dramatic neurologic recovery 9 to 24 hours after rewarming to normothermia and ultimately got discharged with no or minimal neurocognitive decline. Therapeutic hypothermia (32°C– 34°C) has been implemented in animal[58–63] and human trials.[36,38]to decrease the effects of ischemia, anoxia and reperfusion injury on brain tissue. There are two prospective, randomized clinical trials which have demonstrated significant improvement in the neurologic outcome and mortality in patients who

suffered an out-of-hospital ventricular fibrillation cardiac arrest and remained comatose afterregaining of a perfusing rhythm.[36,38] Based on these 2 studies[50,51,64-66]the American Heart Association (AHA) 2005 guidelines had recommended mild hypothermia as a class IIa recommendation for patients who meet the above mentioned criteria. Induction of mild hypothermia is considered potentially beneficial for the patients with non-ventricular fibrillation cardiac arrest, or for in-hospital cardiac arrest (IIbrecommendation).[67]

The role of therapeutic hypothermia is being studied in post trauma and stroke patients. Most studies have failed to show benefit in these patients. However, the role has been well established in post cardiac arrest survivors.Michael Holzer, MD et al[68] meta-analysis which included randomized and quasi-randomized, controlled trials of adults who were successfully resuscitated, where therapeutic hypothermia was applied within 6 hrs after arrival at the emergency department and where the neurologic outcome was compared. They concluded thatmild therapeutic hypothermia improves short term neurologic recovery and survival in patients resuscitated from cardiac arrest of presumed cardiac origin. Its long-term effectiveness and feasibility at an organizational level need further research. Birger Wolff et al[69] conducted a study to evaluate the effect of early achievement of mild therapeutic hypothermia on the neurologic outcome after cardiac arrest. Forty-nine consecutive patients successfully resuscitated from cardiac arrest were enrolled. They concluded that early achievement of mild Therapeutic hypothermia by endovascular cooling appears leads to reduced hypoxic brain injury and a favourable good neurologic outcome after cardiac arrest. Various studies have been conducted for prognostication of patients of post cardiac arrest.

Andrea O et al[70] performed a prospective study named Prognostication after Cardiac Arrest and Hypothermia prospective study to verify the prognostic value of clinical and electrophysiological variables in the TH setting.A total of 111 consecutive comatose survivors of CA treated with TH were prospectively studied over a 3-year period. Neurological examination, electroencephalography (EEG),

and somatosensory evoked potentials (SSEP) were performed immediately after TH, at normothermia and off sedation. Neurological recovery was assessed at 3 to 6 months, using Cerebral Performance Categories (CPC).The presence of at least 2 independent predictors out of 4 (incomplete brainstem reflexes, myoclonus, unreactive EEG and absent cortical SSEP) accurately predicted poor long-term neurological recovery. EEG reactivity significantly improved the prognostication. TH may modify outcome prediction after cardiac arrest, implying that some clinical features should be interpreted with more caution in this setting as compared with the AAN guidelines. EEG background reactivity is useful in determining the prognosis after cardiac arrest treated with TH.

E. Al Thenayan, et al[55] performed a study was to reassess the validity of the various predictors in post-CA patients treated with TIMH. Retrospective chart review of 37 consecutive adults who were comatose after resuscitation from CA and treated with TIMH.They showed that none of six patients without pupillary reactivity, six without corneal reflexes on day 3, or eight with myoclonus status epilepticus recovered awareness. Two of 14 patients with motor responses no better than extension at day 3 recovered motor responses only after 6 days post arrest (one at 5 and one at 6 days post-rewarming) and regained awareness. They concluded that Loss of motor responses better than extension on day 3 was not prognostically reliable after therapeutic induced mild hypothermia for comatose cardiac arrest survivors. None of the patients who lost pupillary or corneal reflexes on day 3 or developed myoclonus status epilepticus recovered awareness.KaWai Cheung et al[71] made a systematic review of randomized controlled trials of therapeutic hypothermia as a neuroprotectant in post cardiac arrest patients. They studied whether induced hypothermia improves neurologic outcome, decreases mortality, or is associated with an increased incidence of adverse events.Pooled data demonstrated that mild hypothermia decreased in hospital mortality (relative ratio [RR] 0.75; 95% confidence interval [CI], 0.62–0.92) and reduced the incidence of poor neurologic outcome (RR

0.74; 95% CI, 0.62–0.84). They concluded that therapeutically induced mild hypothermia decreases in-hospital mortality and improves neurologic outcome in comatose cardiac arrest survivors. The possibility of treatment-limiting side effects cannot be excluded.

Although the therapeutic hypothermia is safe and feasible, yet the potential complications of mild therapeutic hypothermia include renal insufficiency, bleeding, sepsis, and pancreatitis; however, the same complications have also been seen in control groups study by Bernard and colleagues[38] and the HACA group[36]whichreported no significant difference in complications between the two groups. A trend toward bleeding and sepsis in the hypothermia group in the HACA study group. Seizures have also been noted in the normothermia and hypothermia groups, and are mostly secondary to the global ischemic injury that was sustained during the cardiac arrest and reperfusion.[72,73] In the HACA study, they looked for the effect of therapeutic hypothermia on the cognitive functioning and neurophysiologicalsequelae.[36,74]Romergryko G. et al conducted a study which showed that the use of therapeutic hypothermia was not associated with any cognitive decline or neurophysiological deficits.[75] Therapeutic hypothermia has been associated with various adverse effects like arrhythmias, electrolyte imbalance and predisposition to infections. Various studies have shown that it is feasible and not associated with case fatalities. JasminArrich,[76] conducted a study on the clinical application of mild therapeutic hypothermia after cardiac arrest on 650 patients. Of all hypothermia patients, 15 (3%) had an episode of hemorrhage and 28 patients (6%) had at least one episode of arrhythmia within 7 days after cooling. There were no fatalities as a result of cooling. They concluded thattherapeutic hypothermia is feasible and can be used safely and effectively outside a randomized clinical trial. The role of therapeutic hypothermia is being studied in post trauma and stroke patients. Most studies have failed to show benefit in these patients. However, the role has been well established in post cardiac arrest survivors. Since the severity of hypoxic-ischemic brain injury is the major determinant of human survival, most studies

should target in looking at the recovery of neurologic function as the main goal.[77] Death rates related to the withdrawal of life-sustaining therapy (WLST) because of a perceived poor neurologic recovery may reach 81%, regardless of the cause of cardiac arrest.[78]The most common cognitive deficit is memory loss amongst HIE patients who regain consciousness. Delayed recall seems to be particularly impaired.[79,80]Isolated memory loss is relatively uncommon, and the usual pattern of impairment following cardiac arrest combines the memory, executive function, and motor deficits.[81]The speed of cognitive improvement usually reaches a plateau phase at the 3-month markfollowing resuscitation[79,82]; however, prolonged rehabilitation should bepursued as it has been shown to improve the performance in activities of daily living.[83] Two important landmark randomized multicentric studies on humans were done on humans[36,38] in 2002.Considering these results, the 2005 American Heart Association guidelines for cardiopulmonary resuscitation and post resuscitation support concluded that thehemodynamically stable patients who spontaneously develop a mild degree of hypothermia (33°C) post cardiac arrest resuscitation should not be actively rewarmed.[67]These guidelines also state that mild hypothermia may be beneficial for neurologicoutcome and is not associated with significant complications. Nowdays, most of the out-of-hospital cardiac arrest patients are brought to the emergency with non-VF (pulseless electrical activity, asystole) as the initial cardiac rhythm. Some studies focussed on the efficacy and feasibility of hypothermia in other emergency situations and with non VF presentation.[84-86] Bernard et al suggested that it is reasonable to cool most patients with suspected neurological injury after prolonged cardiac arrest irrespective of the initial cardiac rhythm considering the easy management and relatively few adverse effects related to the use of hypothermia.[87]After the negative results of a retrospective study[88] conducted on 491 patients in which the neurologic outcomes did not improve in patients whose initial rhythm was different from VF, further some prospective studies should be conductedto justify the role hypothermia in asystole and pulseless

electrical activity .The following recommendations were made on the basis of the published evidence in October 2002 by the Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation (ILCOR) .

- Unconscious comatose adult patients with return of spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF).
- Such cooling may also be beneficial for in-hospital cardiac arrest patients or other rhythms.

  Hence we will study the role of hypothermia in neurological recovery of post CPR patients. The neurological outcomes would be studied in terms of improvements in the FOUR score, mrs score and CPC scale.

FOUR score

The FOUR Score is a 17-point scale with scores ranging from 0 - 16. Worsening level of consciousness is associated with decreasing FOUR Score .Four domains of neurological function are assessed: eye responses, brainstem reflexes,motor responses, and respiratory pattern. The advantage of this score over GCSis that this clinical grading scaleis used for the assessment of patients with impaired level of consciousness with or without endotracheal intubation.This score has been validated in reference to the Glasgow Coma Scale in various clinical contexts, including assessment by physicians in the Neurocritical Care Unit,[89] intensive care nurses,[90] medical intensive care unit (ICU),[91] and to assess patients in the Emergency Department.[92] Overall, FOUR score has better biostatistical properties than Glasgow Coma Scale in terms of specificity,sensitivity, positive predictive value and accuracy.[93]

Each component of this scale is graded from 0 to 4. During testing of eye response, the subject gets 4 points if able to blink on command, even if the eyelids have to be opened by the examiner, 3 points if the eyelids open but unable to track, 2points if the eyelids are closed but

open in response to loud voice, 1 point if they remain closed but open to pain, and 0 if the eyelids remain closed even in response to pain. In the motor response category, a patient gets 4 points if he is able to make a thumbs-up, fist, or peace sign. There are 3 points for localizing to a painful stimulus,2 points for flexion response ,1 point for an extension response, and 0 point for lack of response or a generalized myoclonusduring evaluation of brainstem reflexes, the patient scores 4 points if both pupil and corneal reflexes are present, 3 points if one pupil is wide and fixed, 2 points if both pupil or corneal reflexes are absent, 1 point if both of those reflexes are absent, and 0 point if both these reflexes are absent along an absent cough reflex. The patient's respiration score is given 4 points if they exhibit a regular breathing pattern and not intubated, 3 points if they exhibit Cheyne-Stokes breathing and not intubated, 2points if they exhibit irregular breathing and not intubated, 1point if they are intubated and breathe above the ventilator rate, and 0 point if they are intubated and breathing at the ventilator rate or apneic

Table 1: FOUR score (Full outline of unresponsiveness)

POINTS	EYE response	Motor response	Brainstem reflexes	Respiration
4	Eyelids open or opened, tracking, or blinking to command	Thumbs up, fist or peace sign	Pupil and corneal present	Not intubated, regular breathing
3	Eyelids open but not tracking	Localizing to pain	One pupil fixed and dilated	Not intubated, cheyne stokes breathing
3	Eyelids closed but open to loud voice	Flexion to pain	Pupil and corneal absent	Not intubated, irregular breathing
1	Eyelids closed but open to pain	Extension response to pain	Pupil and corneal absent	Breathes above ventilator rate
0	Eyelids remain closed with pain	No response to pain or generalized myoclonus status	Pupil, cough and corneal present	Breathes at ventilator rate

Modified rankin score

It is a 6 point disability scale with potential scores ranging from 0 to 6. A score of 6 is given to the patients who expire. The Modified Rankin Score (mRS) is the most commonly used outcome scale in stroke clinical trials

Table 2:Modified rankin score

MODIFIED RANKIN SCALE	
0	no residual symptoms
1	no significant disability; able to carry out all pre-stroke activities.
2	slight disability; unable to carry out all pre-stroke activities but able to look after self without daily help.
3	moderate disability; requiring some external help but able to walk without the assistance of another individual.
4	moderately severe disability; unable to walk or attend to bodily functions without assistance of another individual
5	severe disability; bedridden, incontinent, requires continuous care.
6	Death

Cerebral performance category score

The Cerebral Performance Category (CPC) score is widely used for the research and also quality assurance. (3-5) CPC corresponds to the functional status and quality of life as per the evidence. [94,95]

Table 3: Cerebral performance category score

CPC	
1	Good cerebral performance: Conscious, alert, able to work, might have mild neurologic or psychologic deficit.
2	Moderate cerebral disability: Conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
3	Severe cerebral disability: Conscious, dependent on others for daily support because of impaired brain function.Ranges from ambulatory state to severe dementia or paralysis.
4	Coma or vegetative state: Any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
5	Brain death: Apnea, areflexia, EEG silence, etc.

MATERIALS AND METHODS

SOURCE OF DATA

We conducted a prospective observational study on a total of 20 patients. Those patients who were cardiac arrest survivors and remained comatose post CPR were enrolled in our study. Hypothermia was created using a special blanket/mattress.

METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA

1. Cardiopulmonary Resuscitation (CPR) initiated within 10 minutes of cardiac arrest.
2. Return of spontaneous circulation within 30 minutes of recognition of the cardiac arrest; MAP ≥ 60 for at least 30 minutes post ROSC with or without vasoactive medication.
3. Initiation of Induced Hypothermia within 6 hours of collapse.
4. Initial body temperature must be greater than 30°C.
5. No purposeful movement to command and Glasgow Coma Scale < 6.
6. Age > 18

EXCLUSION CRITERIA

1. Prolonged arrest time longer than 60 minutes or down time without BLS longer than 10 minutes
2. Age less than 18 years, Pregnancy, Uncontrolled bleeding, thrombocytopenia or other coagulopathy
3. DNR or DNI status
4. Refractory arrhythmias

An informed consent was taken from the attendants of the patient. Hypothermia induction was done as per a proper protocol.

Procedure: The provision of therapeutic hypothermia to survivors of cardiac arrest consisted of three phases: Induction, Maintenance and Rewarming.

Induction -It was done using a hypothermia blanketwithin6 hours of collapse

Maintenance with Cooling Blanket Machine

1. Patient temperature was maintained at 33° C for 24 hours from initiation of cooling.
2. Management of hypotension (MAP<80mm Hg), dysarrythmias, electrolyte disturbances was done.

Electrolyte Replacement

1.Electrolytes were checked regularly during the three phases and replacement done as per the need.

2. During cooling phase: we replaced K+ <3.5, Mg++ < 2.0 , ionized Ca++ < 1.0 andCa++ < 7.5

4. We discontinued K replacements 8 hours prior to rewarming

5. We also discontinued Mg and Ca replacements once warming had begun

Rewarming

1. The rewarming process was gradual over 12 or more hours.

2. Target was 37°C over approximately 12 hours

3. We monitored for hyperthermia, hypotension and hyperkalemia

Outcome

Primary outcome was to study the effect of therapeutic hypothermia on the neurological outcome which is assessed by doing neurological examination (four score) and using mRS scale and CPC scale after 48 hours and at the time of discharge or 7 days. Secondary outcome was to see the effect of therapeutic hypothermia on mortality.

Statistical analysis

Data were described in terms of range; mean ±standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the groups was done using Student t-test and *Paired t-test* test. A probability value (*p* value) less than 0.05 was considered statistically significant.All statistical calculations were done using

(Statistical Package for the Social Science)SPSS 21version (SPSS Inc., Chicago, IL, USA)statistical program for Microsoft Windows.

Observation and Results

A total of 28 patients were screen to be included in the study. Out of these 28 patients,8 patients went discharge against medical advice before completing the hypothermia protocol.These patients were excluded from the analysis and final analysis was done on the remaining 20 cases who underwent complete hypothermia as per the protocol. The mean age of the patients was 64.4±11 years. Out of the 20 patients, 8(40%) patients belong to the age group of 61 to 70 years while 7(35%) patients belong to the age group of less than 60 years,4(20%) were of the age group of 71 to 80 years while only 1(5%) patients were of the age group of greater than 80 years.

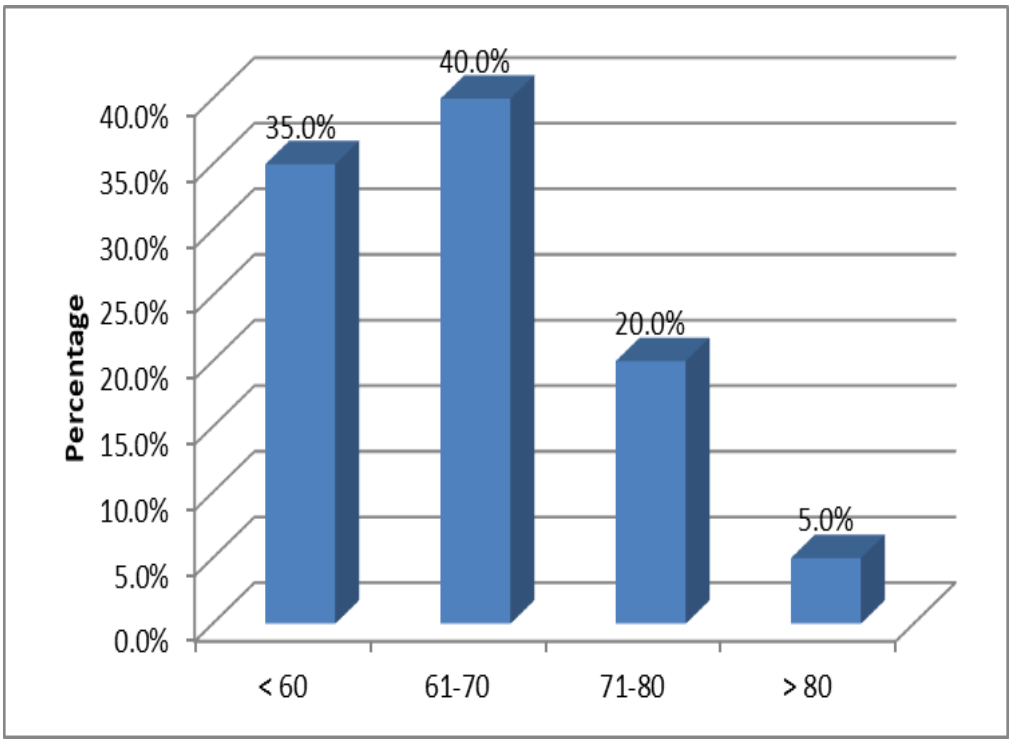

FIGURE1: Age wise distribution of patients.

In this study, 70% (n=14)of patients were males and 30%(n=6) of patients were females.

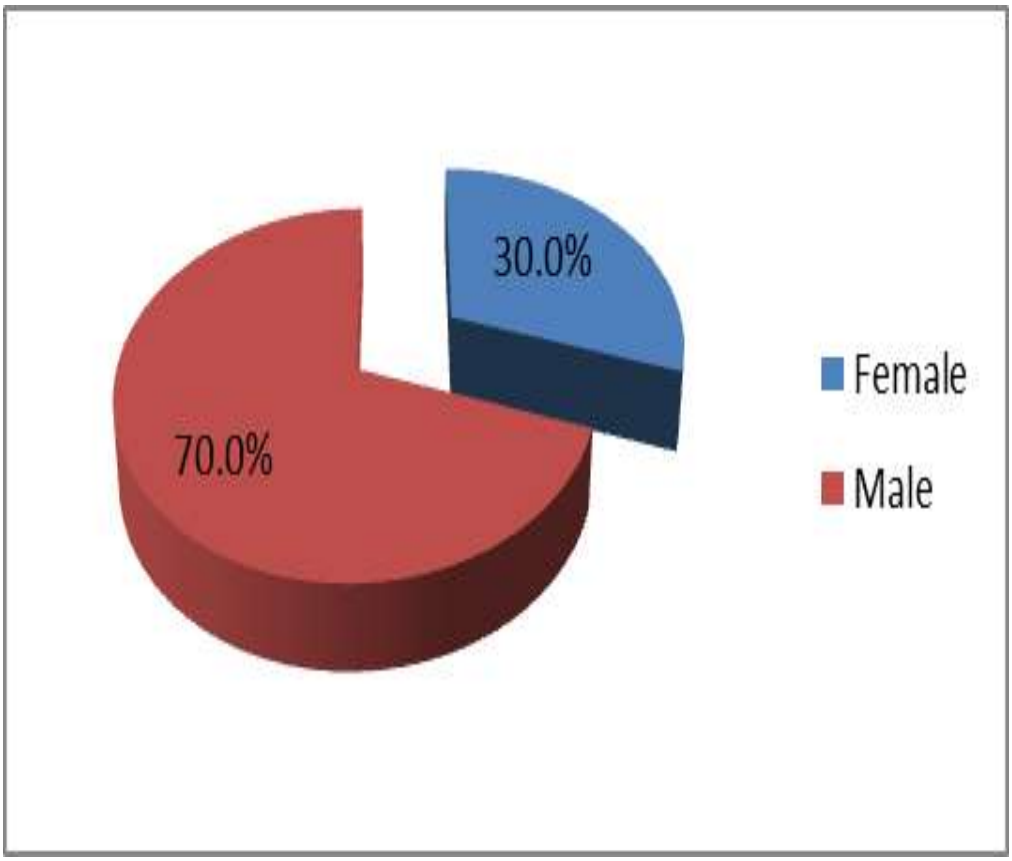

FIGURE 2: Sex distribution of patients.

Previous studied had shown that hypothermia is also useful in the patients who suffer out-of-hospital cardiac arrest. In our study, we had included both the out-of-hospital cardiacarrest as well as inhospital cardiac arrest survivors. We observed that 9 (45%) patients had arrest athome while the rest 11(55%) suffered from cardiac arrest within the hospital.

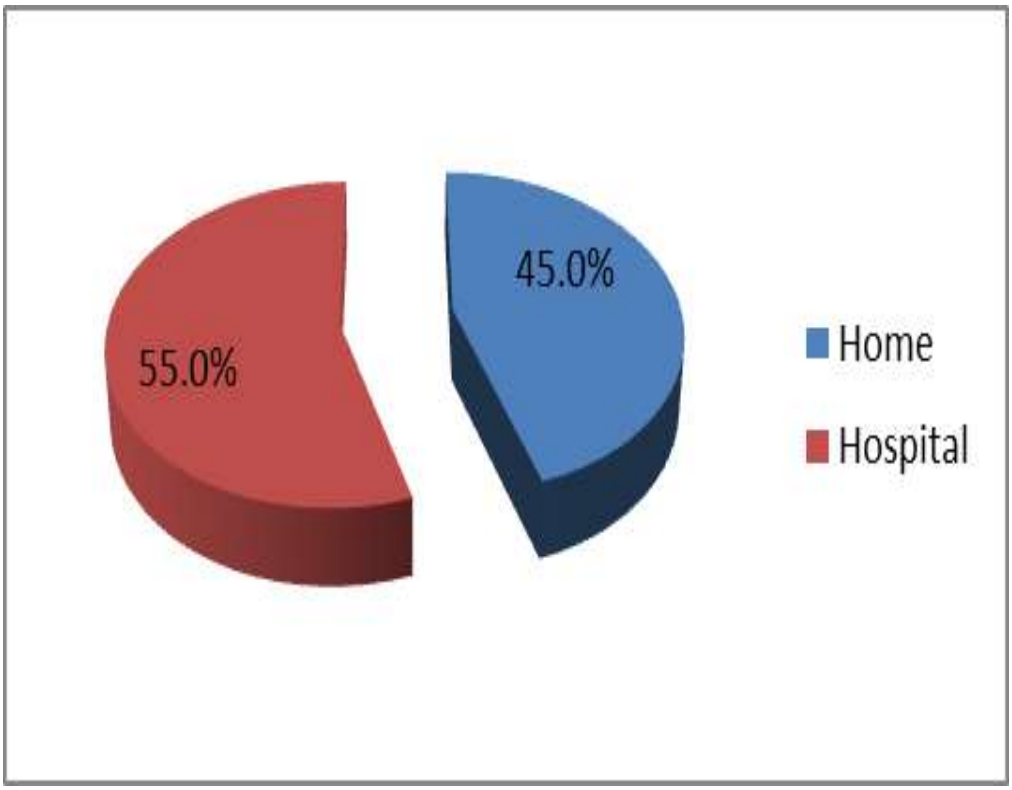

FIGURE 3: Pie chart depicting the place of cardiac arrest.

The patients who suffered cardiac arrest were suffering from one or more comorbid condition.The comorbidities most commonly observed were DM, HTN, cardiac and cerebrovasculascular in 12(60%), 11(55)%, 15(75%) and 3(15%) patients respectively.

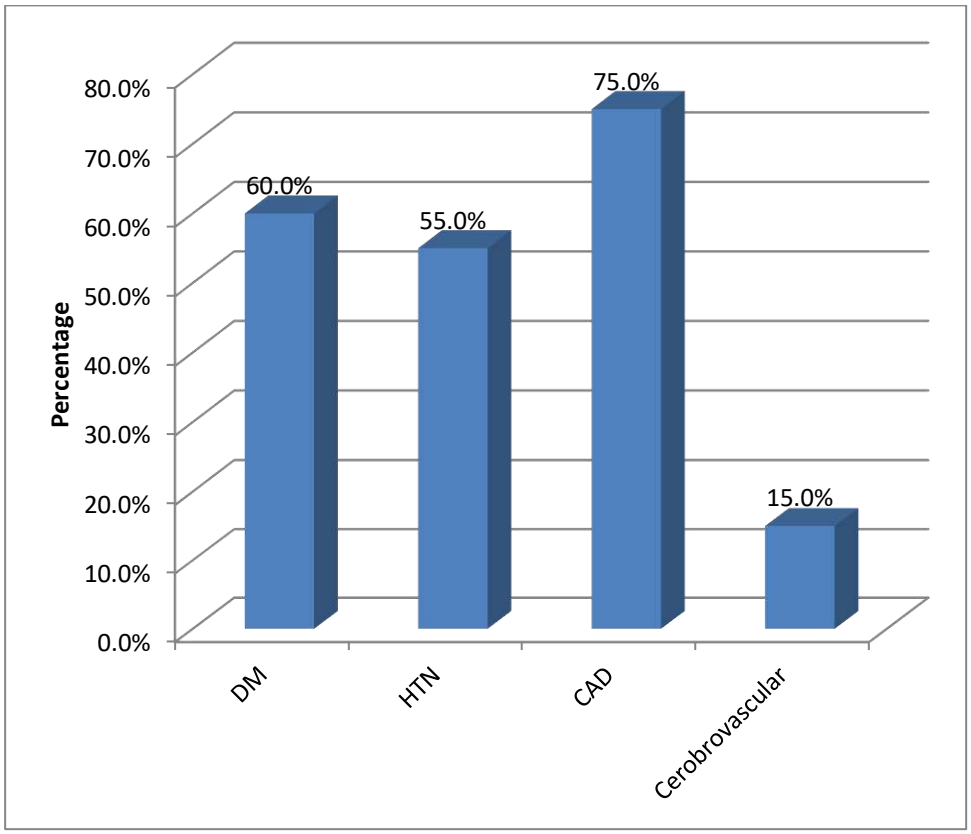

Figure4: Distribution of comorbidities seen in our patients.

We kept the record of two important time limits. One of these is the time of initiation of CPR post cardiac arrest. The mean value of time of initiation of CPR post cardiac arrest was 3.8±4.2 minutes.It was observed that in 11(55%) patients,CPR was initiated within 3 minutes of cardiac arrest.In 6 (30%) patients it was initiated after 8 to 10 minutes of cardiac arrest while in the rest 3(15%) of the patients, it was started within 4 to 7 minutes of cardiac arrest.

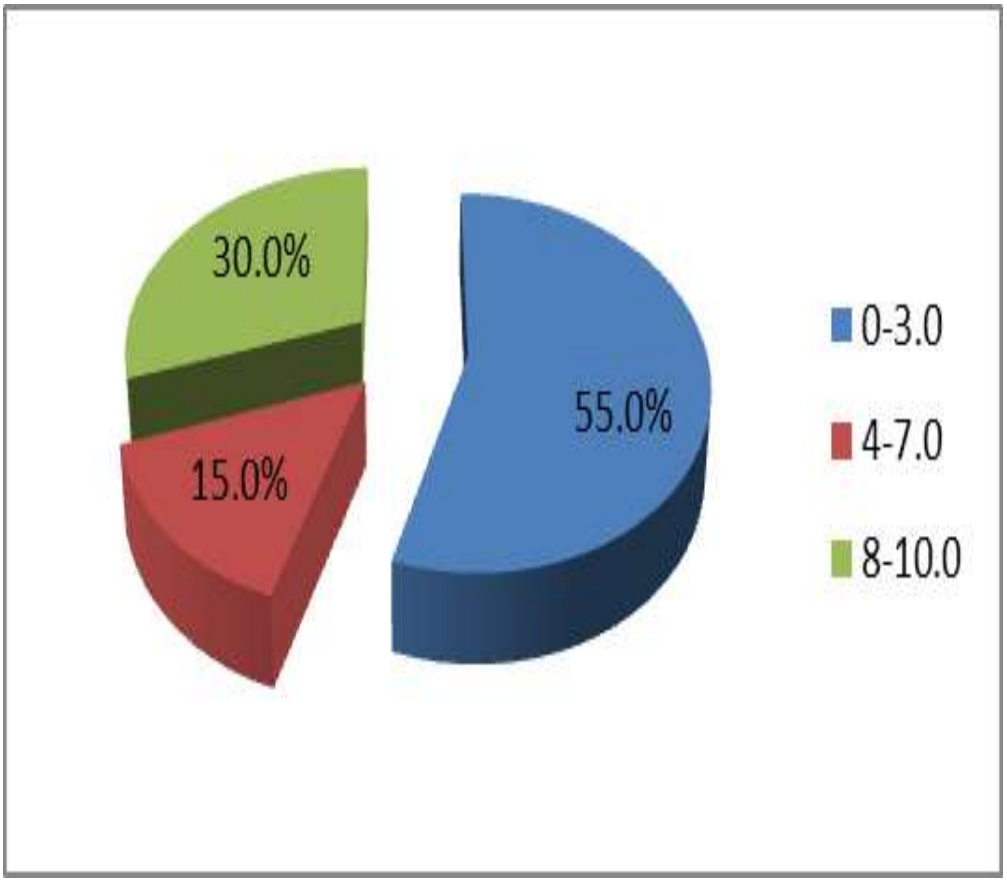

FIGURE 5: Pie chart depicting the time of initiation of CPR post cardiac arrest.

The time taken for restoration of spontaneous circulation was also noted after cardiopulmonary arrest.The mean value was 17.2±8.8 minutes.The time taken was less than 10 minutes in 5(25%),10-20minutes in 9(45%) and 20-30 minutes in 6(30%) patients.

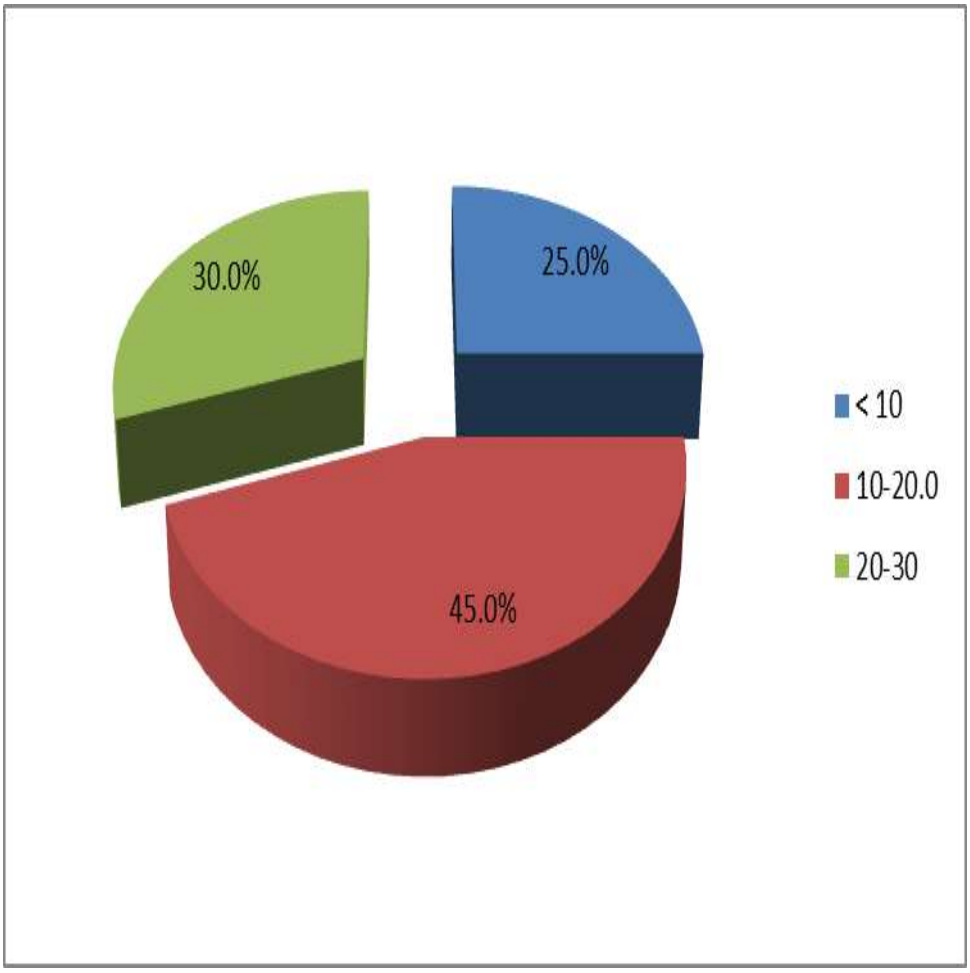

FIGURE6: Pie chart showing the time taken for ROSC after cardiac arrest.

We compiled the demographic variables in the following table

Table 4: Basic demographic data in our patients.

AGE (years)	No. of cases (n=20)	Percentage
< 60	7	35.0%
61-70	8	40.0%
71-80	4	20.0%
> 80	1	5.0%
Mean± SD	64.4 ± 11.0 years	
GENDER		
Female	6	30.0%
Male	14	70.0%
REASON FOR ADMISSION		
Breathlessness	6	30.0%
chest pain	3	15.0%
Headache, Vomiting	2	10.0%
Unresponsiveness	9	45.0%
Comorbidity		
DM	12	60.0%
HTN	11	55.0%
CAD	15	75.0%
Cerobrovascular	3	15.0%
CAUSE OF ARREST		
Arrythmias	9	45.0%
Cardiogenic shock	6	30.0%
Hypoxic	4	20.0%
Septic shock	1	5.0%
Total	20	100.0%
PLACE OF ARREST		
Home	9	45.0%
Hospital	11	55.0%
Time of arrest-Time of initiation of CPR	3.8± 4.2 minutes	
Time of initition of CPR-ROSC TIME	13.4 ± 7.1minutes	

In our study, the most common complications were sepsis, arrhythmias hyperglycemia and hypokalemia. 70% of patients who underwent hypothermia landed up with sepsis ,65% of the patients had arrhythmias, hyperglycemia was reported in 65% of the patients and another 50% suffered from hypokalemia during the in the process.Hypokalemia was seen in 20% of the patients while hypocalcemia and hypomagnesemia was seen in 5% of the patients.

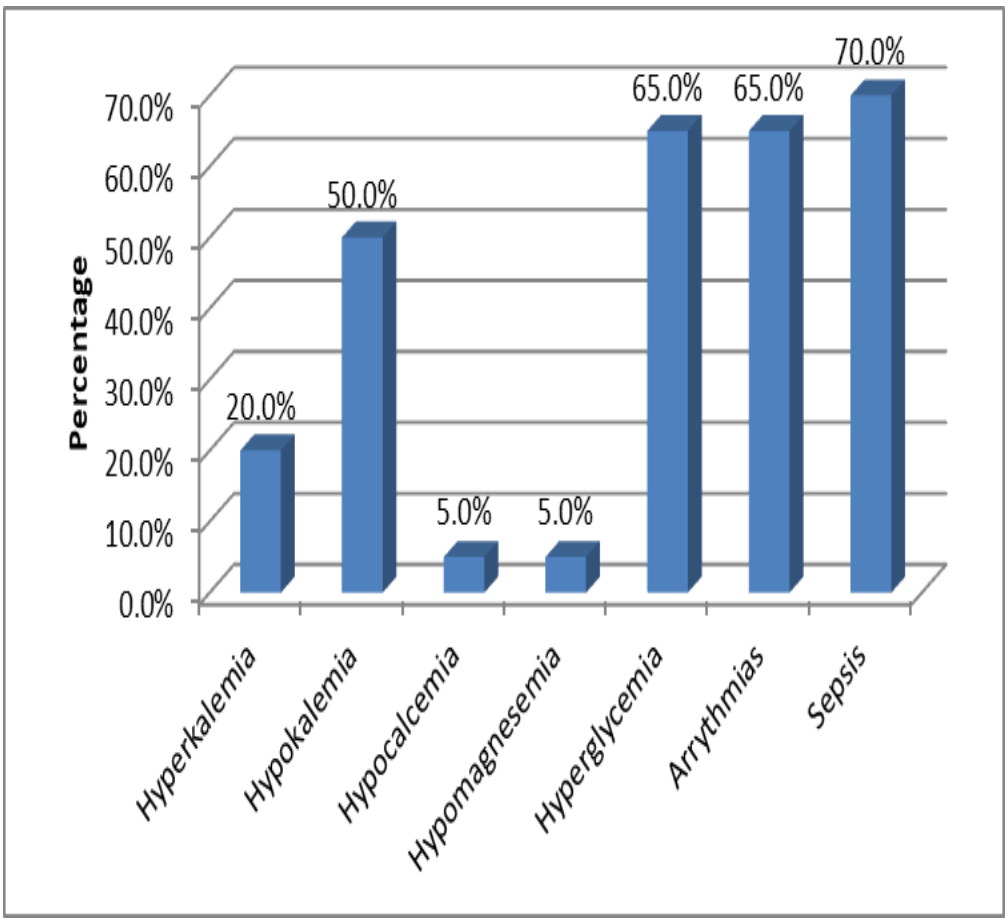

FIGURE 7: Distribution of various complications due to hypothermia in post CPR patients.

We further stratified these complications according to the phases in which they occurred.During the induction phase the most common complications were electrolyte imbalance.Majority of the electrolyte disturbances occur during the Induction plate.All the cases of hypocalcemia and hypomagnesemia,60% of the cases of hypokalemia,53.8% cases of hyperglycemia occurred during the induction phase.

During the maintenance phase, arrhythmias and sepsis were noted in 92.3 percent and 57.1% respectively. Hypokalemia were seen in 40% during the maintenance phase.During the rewarming phase, the major complication observed was hyperkalemia.

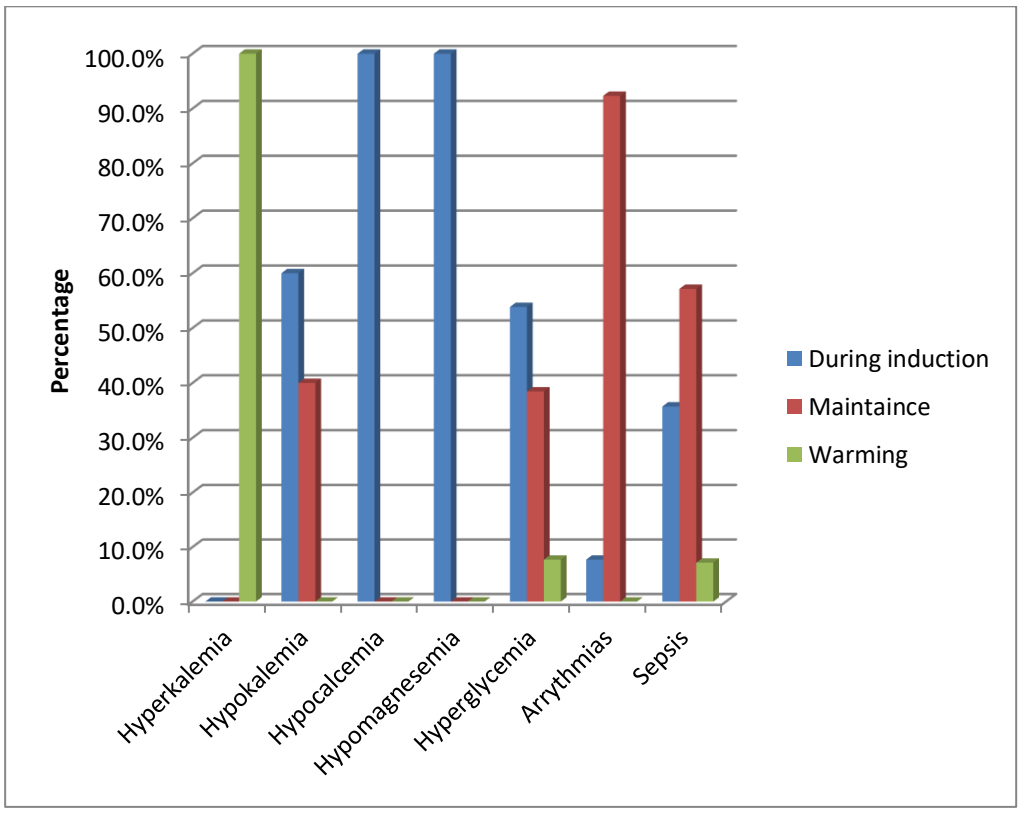

FIGURE 8: Distribution of various complicationsduring induction, maintenance and warming phase of hypothermia in post CPR patient.

The majorityof the patientsi.e 13(65%) had a hospital stay duration of less than one week while the rest 7(35%) of the patients had a longer duration of hospital stay of more than 1 week. The mean hospital stay of our patients was 11.9±12.3 days.

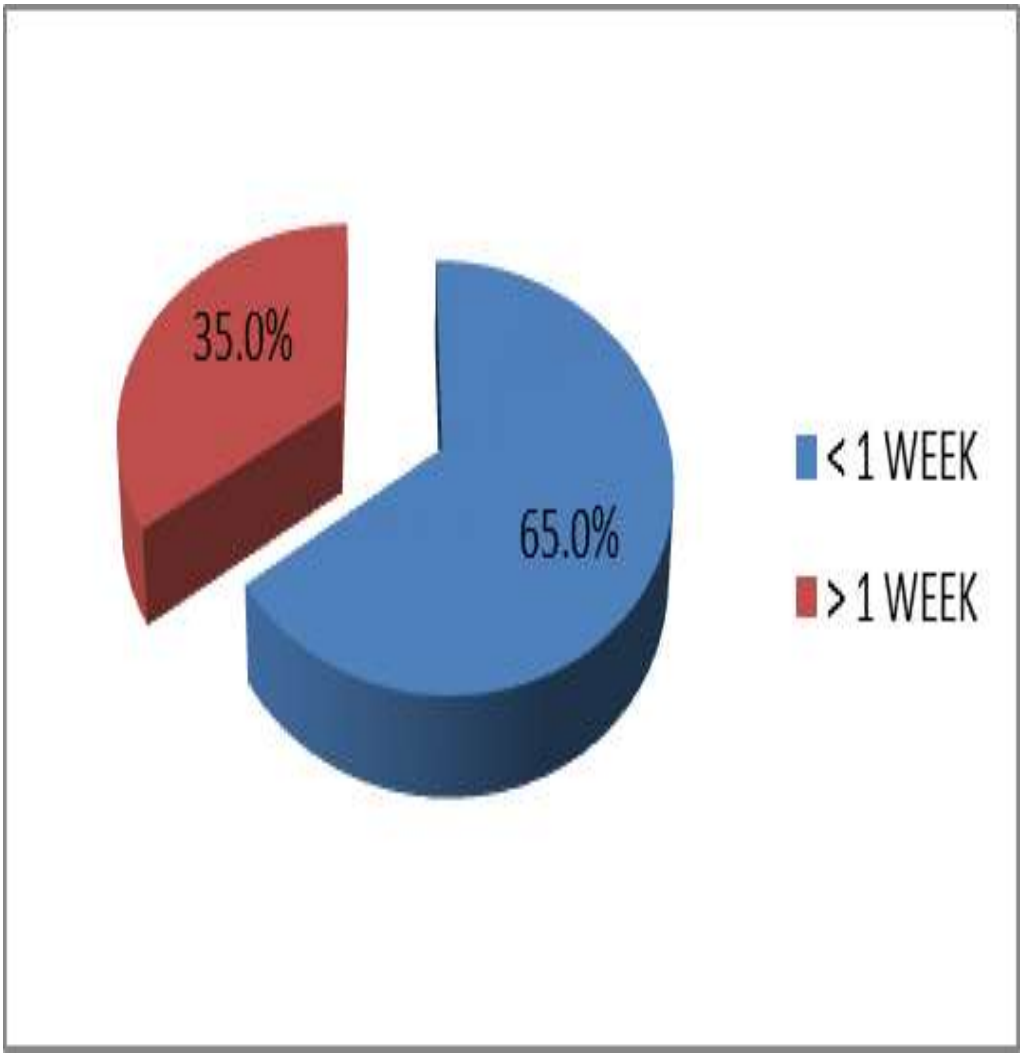

FIGURE 9: Distribution of hospital stay of the patient.

The outcomes of the patients who underwent hypothermia post cardiopulmonary resuscitation were as follows:

40%(n=8) of the patients got discharged, 40% (n=8)died while the rest (n=4)20% went discharge against medical advice.These DAMA patients were telephonically contacted and all of them had died on the way to their homes.

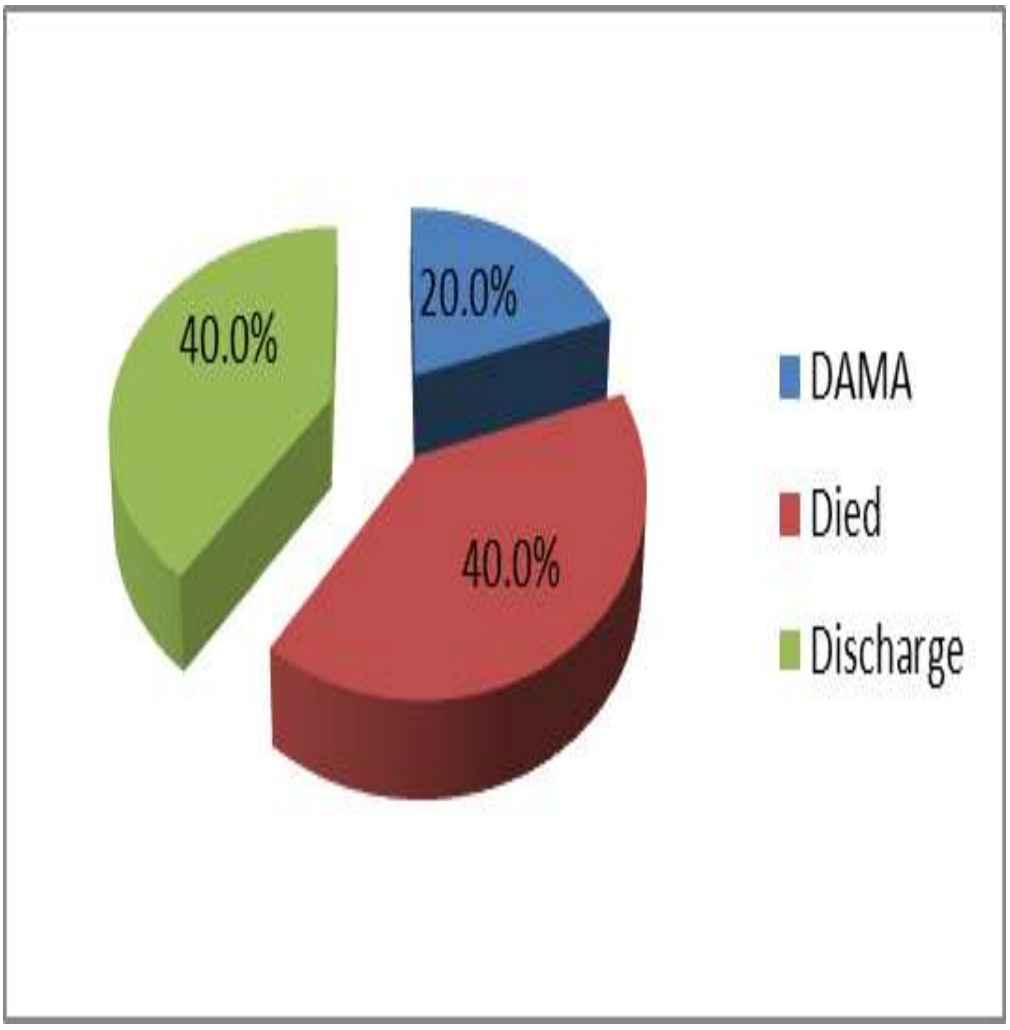

FIGURE10: Outcome of post CPR patients who were given hypothermia.

We studied the neurological outcomes as per the improvement in three scales: four score, mRS scale and cerebral performance category scale at baseline and 48 hours.We observed that the mean FOUR score at baseline was 3±1.257 while at 48 hours was 4.45±3.187. There was a trend towards improvement from the baseline post application of hypothermia although the value is non-significant . The mean mRS and CPC at baseline were 5±0 and4.5± 0.22 and did not change at 48 hours.

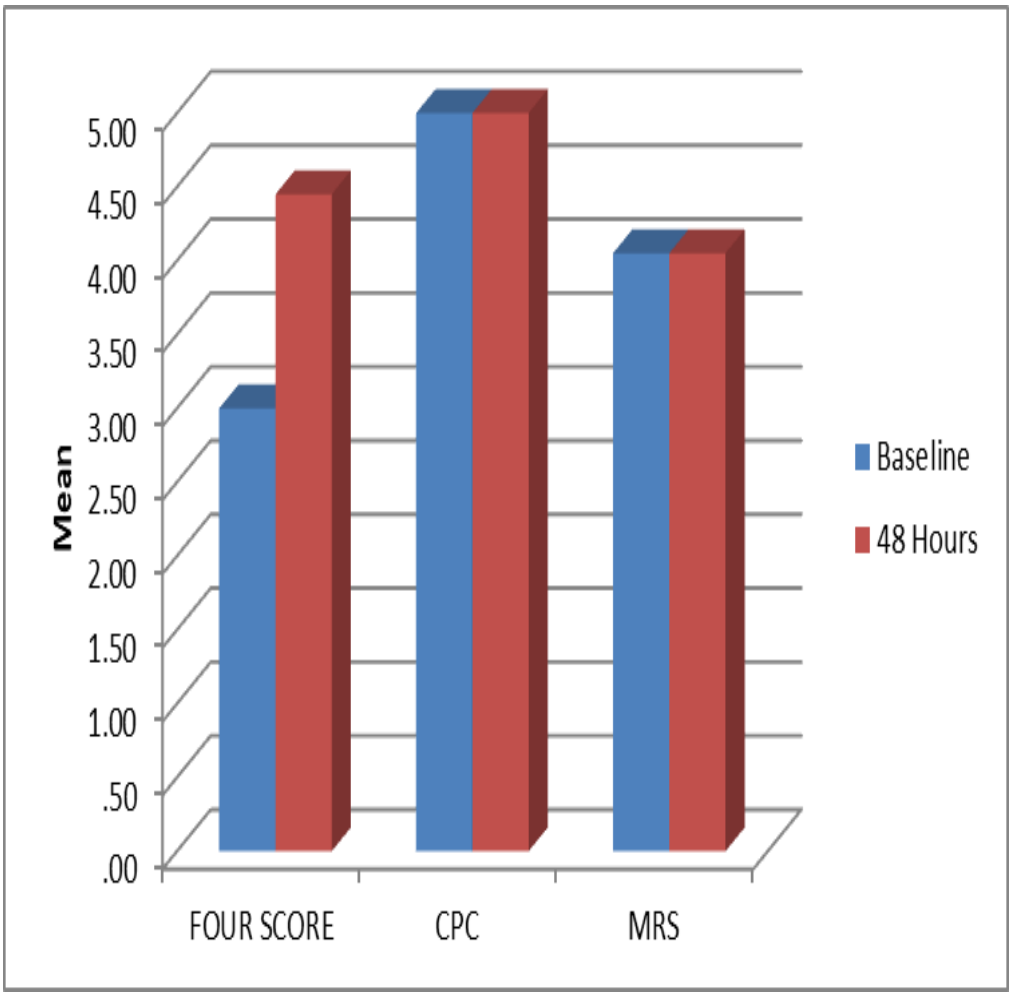

FIGURE11: Mean FOUR score, mRS and CPC at baseline and 48hours .

We further compared these FOUR score, mRSscore and CPC score at baseline and outcome.We observed that the mean FOUR score at baseline was 3±1.26 while at outcome it was 5.1±5.75. There was a trend towards improvement from the baseline post application of hypothermia although the value is non-significant (p value=0.086). The mean mRS at baseline and outcome was 5±0 and 4.9±1.07 while the mean CPC values at baseline and outcome was 4.05±0.22 and 3.95±1.1 respectively.

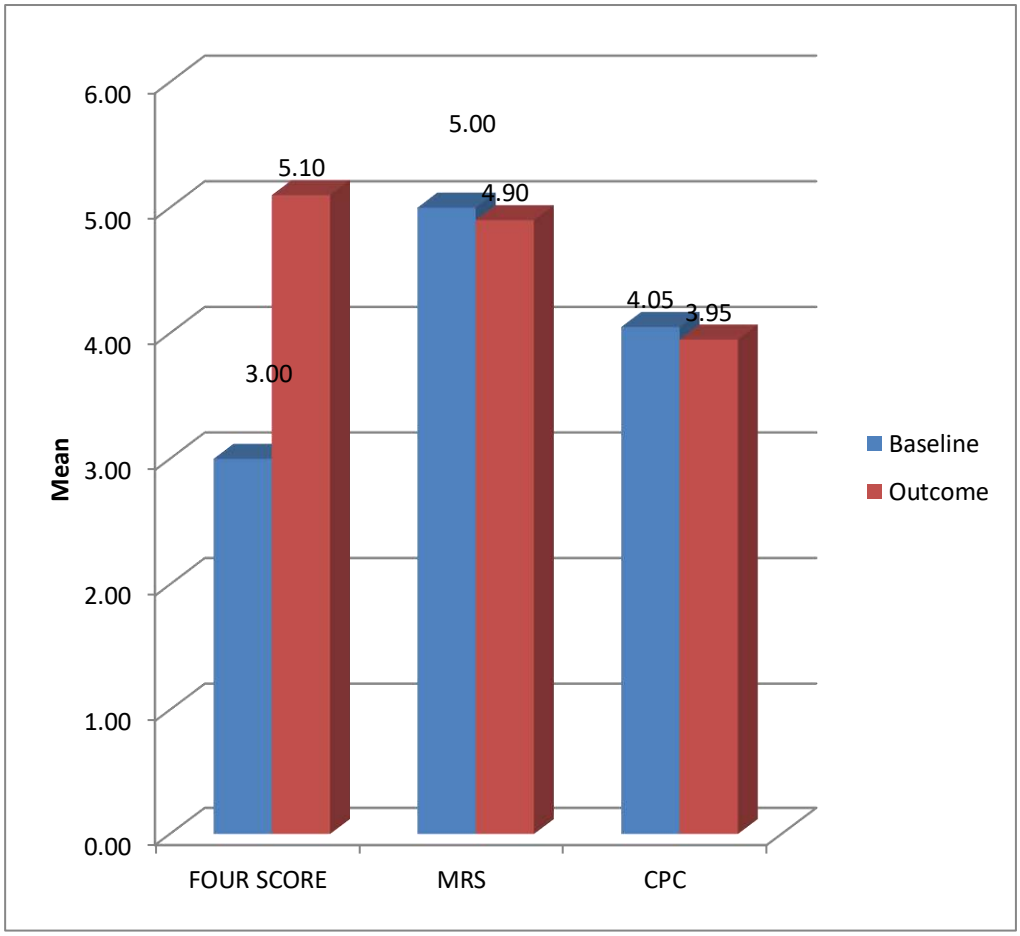

FIGURE12: Mean FOUR score, mRS and CPC at baseline and outcome

We compared these three scales at the baseline as well as at the outcome. We observed that FOUR score improved in 8(40%)patients, got worse in 9(45%) patients and did not change in 3(15%) patients. It was also observed that modified ranking score improved in 8(40%), worsened in8(40%) and remained the same in rest 4(20%).Similarly the improvement in cerebral performance category scale was also assessed. The CPC scale improved in 8(40%), worsened in 8(40%)and did not change in 4(20%) as compared to the baseline.

Table 5: Trend of FOUR score, mRS score and CPC score at baseline and outcome (I= Improved, N= none and W= worse)

	FOUR SCORE		**MRS**		**CPC**	
	No. of cases	%	No. of cases	%	No. of cases	%
I	8	40.0	8	40.0	8	40.0
N	3	15.0	4	20.0	4	20.0
W	9	45.0	8	40.0	8	40.0
Total	20	100.0	20	100.0	20	100.0

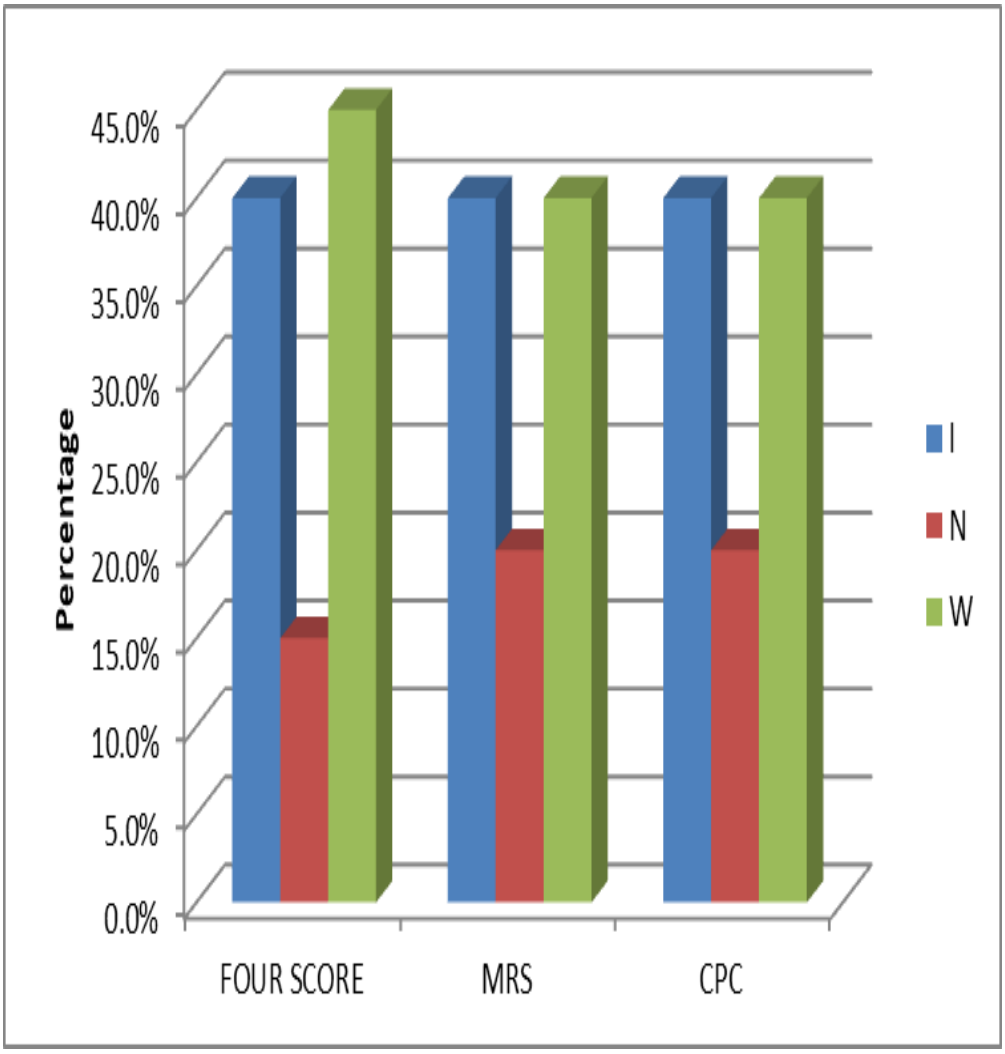

Figure 13: Trend of FOUR score, mRS score and CPC score at baseline and outcome. (I= Improved, N= none and W= worse)

In our study, we further analysed the individual components of FOUR score at the baseline and outcome of all the 20 patients. The mean values of Eye response, Motor response, Brainstemreflexes, Respiration were 0.15±0.37,05±051,1.35±0.59 and1.0±0.56 while at outcome the mean values were 0.9±1.21,0.7±0.98, 1.75±1.92 and 1.75±1.92 respectively.

Table 6: Mean values of components of FOUR score at the baseline and outcome

n=20	**Baseline**		**Outcome**		t	p-value
	Mean	Std. Deviation	Mean	Std. Deviation		
Eye response	0.15	0.37	0.90	1.21	-2.881	0.010
Motor response	0.50	0.51	0.70	0.98	-0.890	0.385
Brainsteam reflexes	1.35	0.59	1.75	1.92	-0.914	0.372
Respiration	1.00	0.56	1.75	1.92	-1.891	0.074

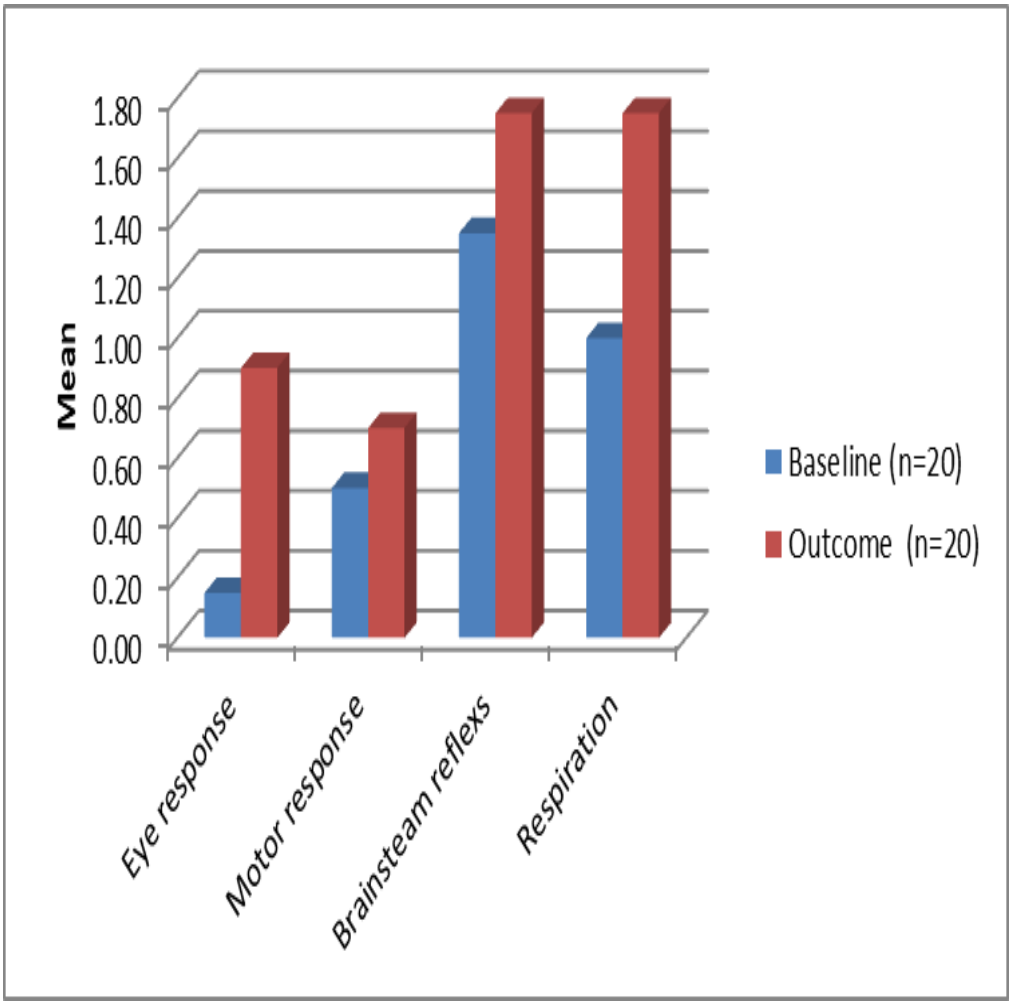

Figure 14 a:Mean values of components of FOUR score at the baseline and outcome.

We found that in the patients who survived, mean values of the respiratory system and brainstem reflexes had shown maximum improvement at outcome as compared to the eye and motor response. The mean of respiration and brainstem reflexes were 4±o while the mean of eye response and motor response at outcome was 2.13±0.99 and 1.63±0.92 respectively while at baseline these were 1.25±0.46 ,1.38±0.52, 0.38±0.52 and 0.75±0.46 for respiratory pattern, brainstem reflexes, eye and motor response respectively.

Table 6b: Mean values of components of FOUR score at the baseline and outcome in the patients who got discharged.

n=8	**Baseline**		**Outcome**		t	p-value
Discharge	Mean	Std. Deviation	Mean	Std. Deviation		
Eye response	0.38	0.52	2.13	0.99	-3.862	0.006
Motor response	0.75	0.46	1.63	0.92	-1.986	0.087
Brainsteamreflexes	1.38	0.52	4.00	0.00	-14.346	0.000
Respiration	1.25	0.46	4.00	0.00	-16.803	0.000

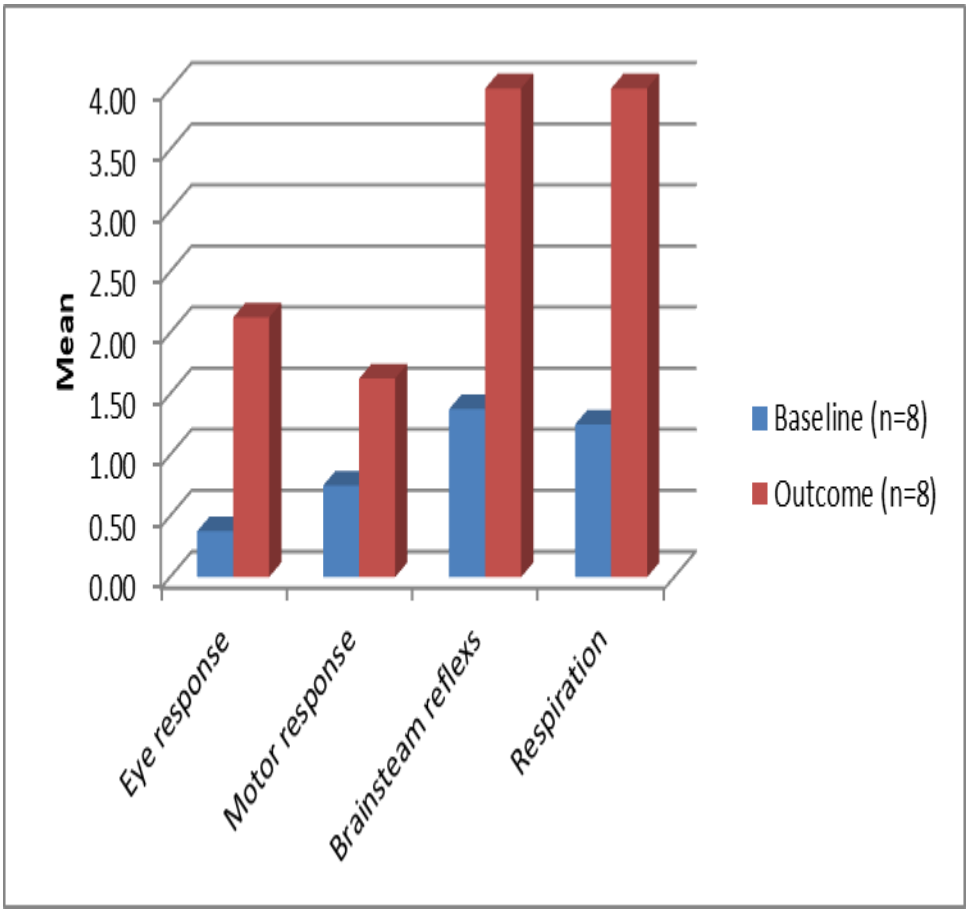

Figure 14 b: Mean values of components of FOUR score at the baseline and outcome in the patients whogot discharged.

We divided the study patients into two groups: group 1- out of hospital cardiac arrest (home) and group 2- in hospital cardiac arrest survivors. We compared the demographic data of patients of group 1 and 2. We observed that the mean age of the patients was higher (68.6 ± 10.4) in group 1 as compared to group 2(60.9±10.67). The mean hospital stay was 15±14.05 and 9.45±10.67 respectively. The mean values of time of arrest to initiation of CPR and restoration of spontaneous circulation was higher (8.22±1.48 and 23.33±4.8) in group 1 as compared to group 2(0.18±0.4 and 12.18±8.21) respectively. We also observed that time to initiation of CPR to return of spontaneous circulation was 15.11±5.11 and 12±8.37 respectively.

Table 7: Comparison of baseline variables of patients of two groups

	Group 1		**Group 2**		t	p-value
	Mean	SD	**Mean**	**SD**		
AGE (years)	68.67	10.43	**60.91**	**10.67**	1.634	0.120
Hospitalstay	15.00	14.05	**9.45**	**10.72**	1.002	0.330
TIME OF ARREST-TIME OF INITIATION OF CPR	8.22	1.48	**0.18**	**0.40**	17.324	0.000
TIME OF ARREST-ROSC TIME	23.33	4.80	**12.18**	**8.21**	3.594	0.002
TIME OF INITIATION OF CPR-ROSC TIME	15.11	5.11	**12.00**	**8.37**	0.974	0.343

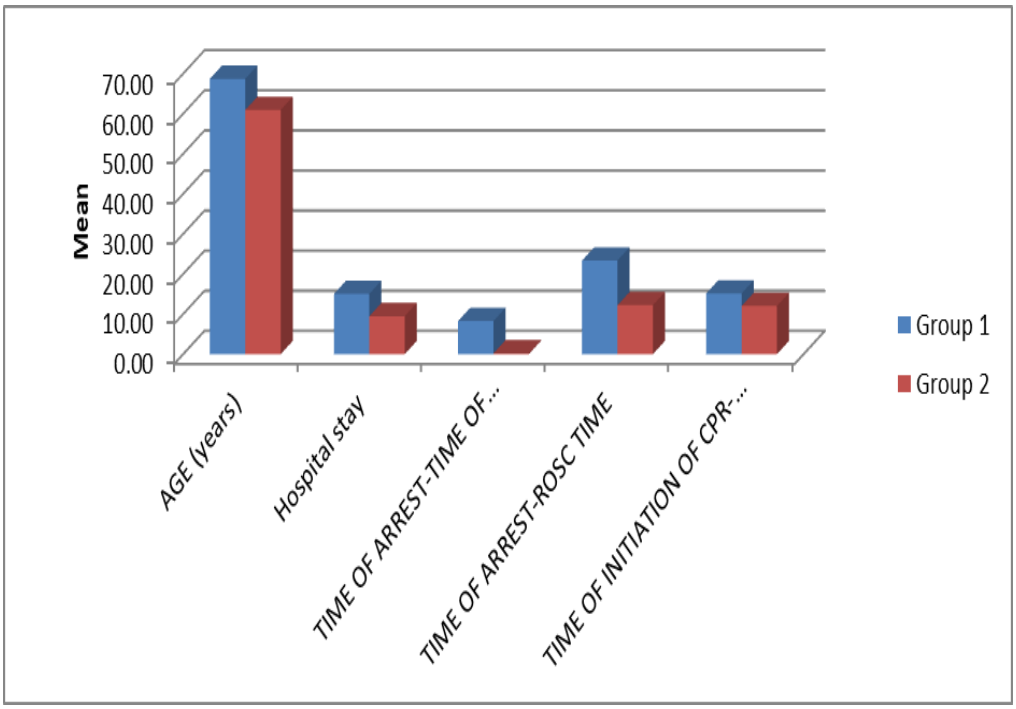

Figure 15: Comparison of baseline variables of patients of two groups

Group 1- Home (out of hospital cardiac arrest)

Group 2- In hospital cardiac arrest survivors

We further analysed the reason of admission, cause of arrest and outcome of two groups.

Table 8: Comparison of reason for admission, cause of arrest and outcome of 2 groups(home vs hospital)

						Total
		Group 1		**Group 2**		
REASON FOR ADMISSION	Breathlessness	2	22.2%	4	36.4%	6
	chest pain	0	0.0%	3	27.3%	3
	Headache, vomittimg	0	0.0%	2	18.2%	2
	Unresponsiveness	7	77.8%	2	18.2%	9
CAUSE OF ARREST	Arrythmias	7	77.8%	2	18.2%	9
	Cardiogenic shock	1	11.1%	5	45.5%	6
	Hypoxia	1	11.1%	3	27.3%	4
	septic shock	0	0.0%	1	9.1%	1
OUTCOME	Died	4	44.4%	8	72.7%	12
	Discharge	5	55.6%	3	27.3%	8

Amongst the total 9 patients who belonged to group 1, the reason for admission were as follows: breathlessness in 2 (22.2%) and unresponsiveness in 7(77.8%). However, for group 2(n=11), the reasons for admission were breathlessness, chest pain, headache, vomiting and unresponsiveness in 36.4%, 27.3%,18.2% and 18.2% patients respectively.

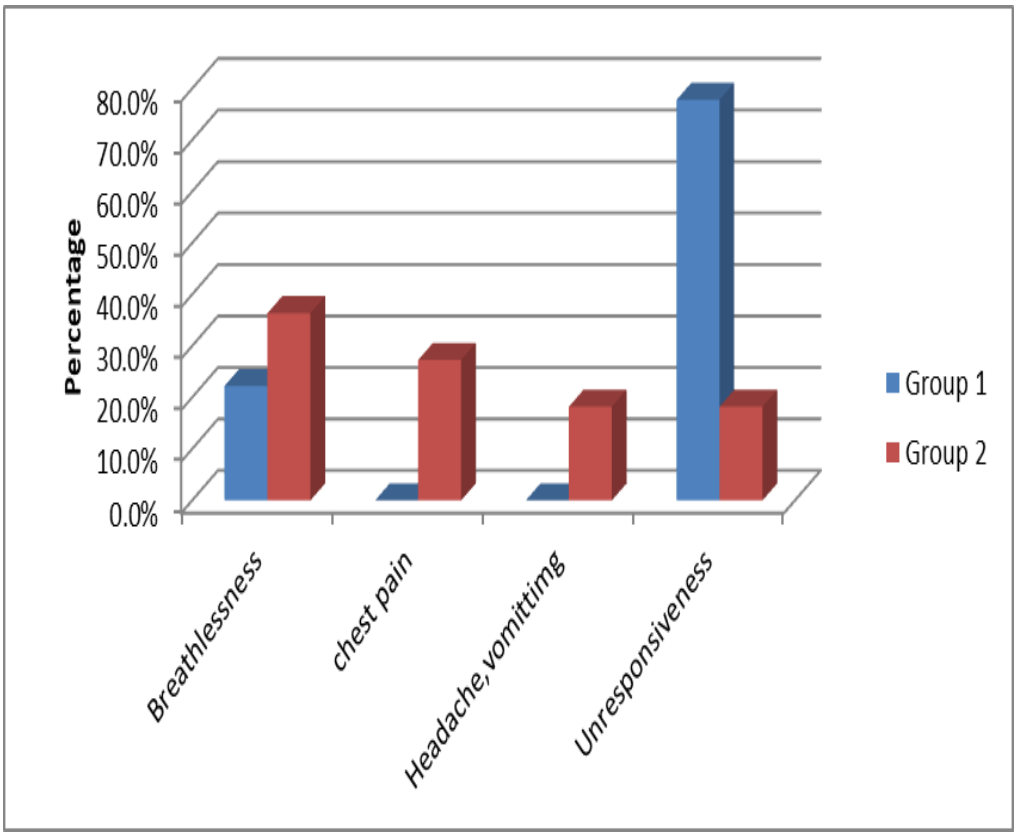

Figure 16a: Reason of admission in out of hospital (Group 1) versus in hospital cardiac arrest survivors (Group 2).

The major cause of arrest for group 1 was arrhythmias seen in 77.8% patients as compared to group 2 (18.2%) with a significant p value of 0.007. The other causes of arrest were cardiogenic shock, hypoxia and septic shock seen in 11.1%, 11.1% and 0% patients of group 1 and 45.5%, 27.3% and 9.1% of the group 2 patients.

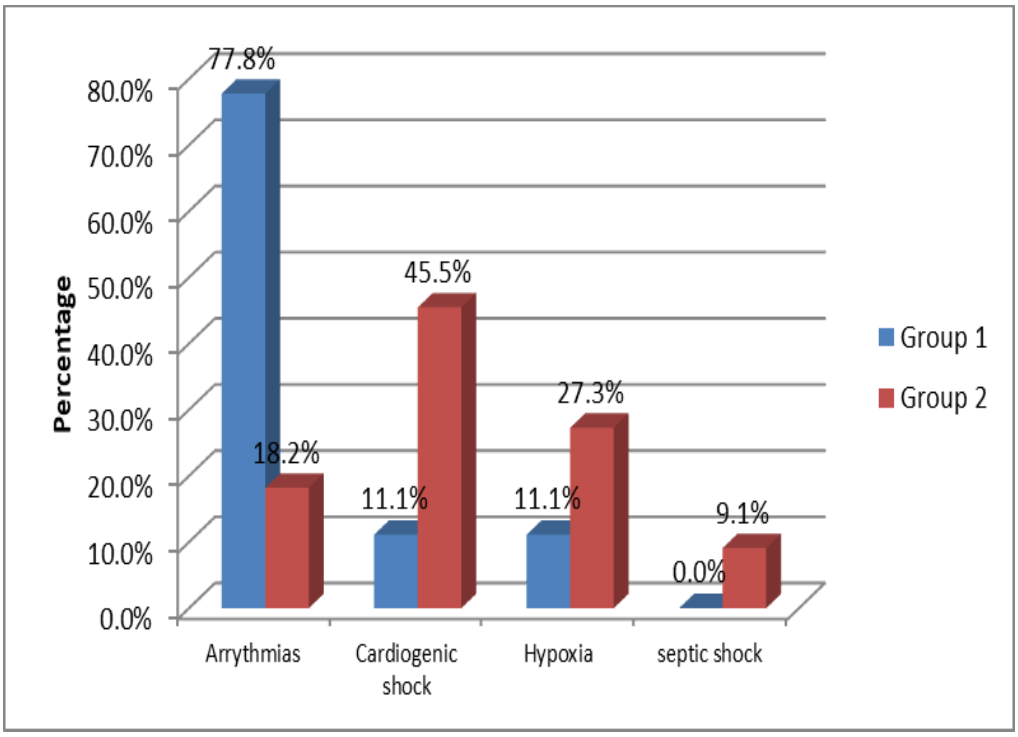

Figure 16 b: Bar graph showing cause of arrest in group 1 and group 2.

In our study, we found that the death rate was 44.4% and 72.7% in group 1 and 2 respectively. The number of patients who survived was higher in group 1(55.6%) as compared to group 2(27.3%)

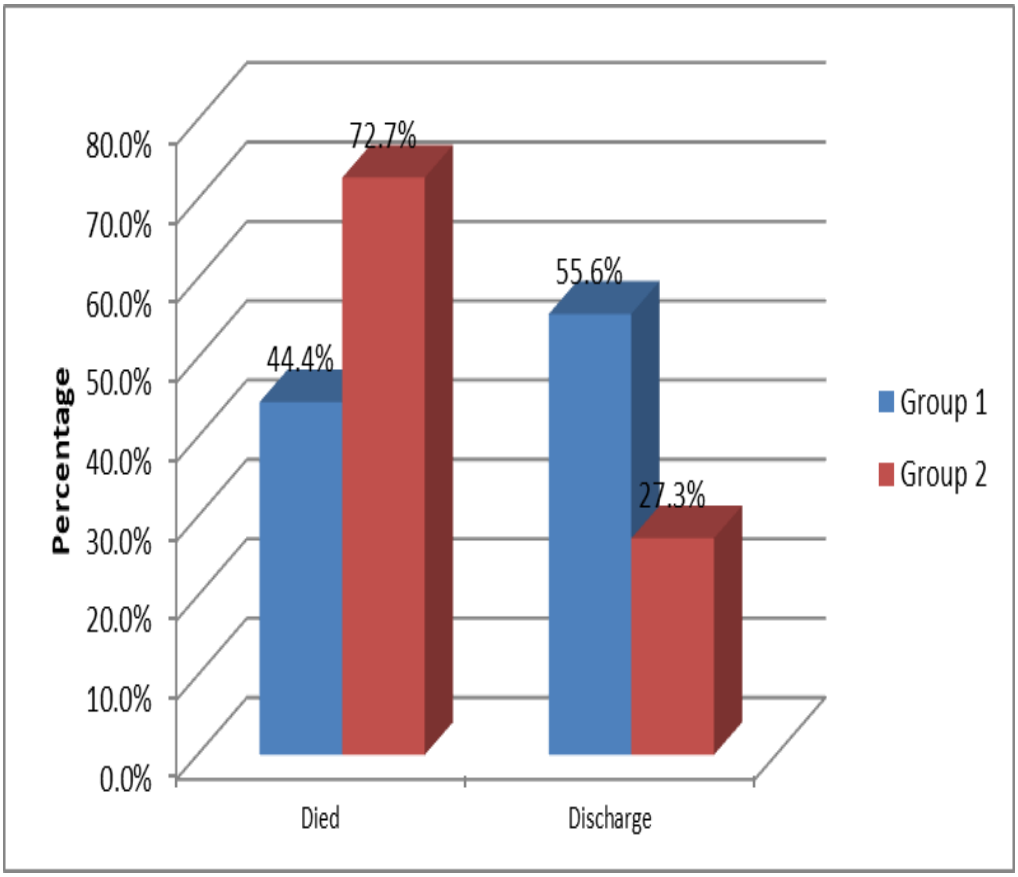

Figure 16c: Figure showing outcome of patientsin group 1 and 2.

In our study,we also compared the neurological outcomes of two groups. There was a trend towards improvement of FOUR score, CPC and mRS scale in patients of group 1 (out of hospital cardiac arrest survivors) vs group 2 (in hospital cardiac arrest). The mean values of FOUR score, mRS score and CPC scale at baseline and outcome in patients of group 1were 3.67±0.87 and 6.89±5.75; 4±0 and 3.4±1.13;5±0 and 4.44±1.13 respectively while in group 2, the mean values were 2.45±1.29and 3.64±5.57; 4.09±0.3 and 4.36±0.92; 5±0 and 5.27±0.9 respectively.

Table 9: Comparison of FOUR score, mRS and CPC at baseline and out outcome in group 1vs group 2 patients.

	Group 1		Group2		t	p-value
	Mean	**SD**	**Mean**	**SD**		
FOUR SCORE_Baseline	3.67	0.87	2.45	1.29	2.40	0.027
FOUR SCORE_Outcome	6.89	5.75	3.64	5.57	1.28	0.217
CPC_Baseline	4.00	0.00	4.09	0.30	-0.90	0.380
CPC_Outcome	3.44	1.13	4.36	0.92	-2.00	0.060
MRS_Baseline	5.00	0.00	5.00	0.00		
MRS_Outcome	4.44	1.13	5.27	0.90	-1.82	0.085

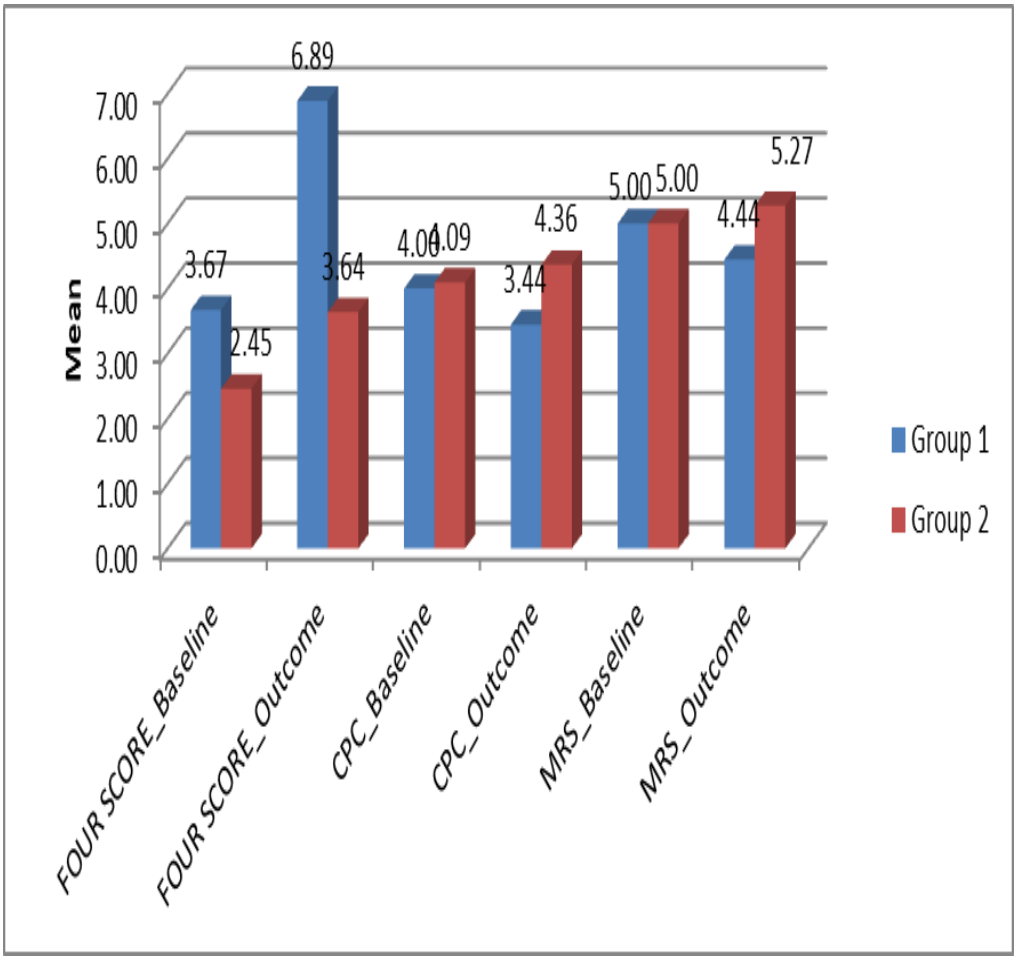

Figure 17: Comparison of FOUR score, mRS and CPC at baseline and outcome in home vs hospital cardiac arrest patients.

DISCUSSION

We conducted an observational study on the role of hypothermia on neurological recovery and survival of 20cardiac arrest comatose survivors in a tertiary care centre.The demographic characters of our patients were as follows:the mean age of the patients was 64.4 ±11 years which was comparable to the Bernard study group in which the mean age was 66.8 years and 65 years in the normothermia and hypothermia groups respectively.In our study ,majority (70%) of the patients were males and 30 % patients were females which is similar to gender difference trend seen in both the Bernard and HACA study.The commonest comorbidities observed in our study group were diabetes mellitus(60%), hypertension(55%) and coronary artery disease(75%)and cerebrovascular accident (15%). This is in contrast to the HACA study in which diabetes, coronary heart disease, cerebrovascular accident was present in 8%,32% and 7% of patientsrespectively.The mean time of initiation of CPR and restoration of spontaneous circulation after cardiac arrest were3.8± 4.2 and 17.2 ± 8.2respectively which are lesser as compared to the Bernard study group in which the mean times were 8.3±2.8 and 25±8.9 respectively. This difference can be explained by the fact that in our study we included patients who suffered in hospital cardiac arrest also in whom the CPR could be initiated as soon as possible in a few seconds in the ICU setting . In our study, the major cause of arrest was arrythmias seen in 45% patients,cardiogenic shock in 30%, hypoxia in 20% and septic shock in 5%. The mean duration of hospital stay in our patients was11.9±12.3 days. In our study group, the outcome of the patients was as follows- 40% got discharged, 40%died and 20%took discharge against medical advice(DAMA). The relatives of the patients who went DAMA were retrospectively contacted and all of them had died on their way to home. Thus, in our study the overall survival rate was 40% out of the total 20 patients who received hypothermia. These results **slightly dif**fer from **Bernard (**Australian**) and HACA (European)** trial of hypothermia in which the survival rates were almost 49% **and 59%**

respectively.Both HACA and Bernard studies were multicentric case control studies in out of hospital cardiac arrest patients in whom the cause of arrest was ventricular fibrillation.Thus ,there is difference in the overall survival rate that is 40% in our study as compared to 49% and 59% in the Bernard and HACA group respectively. This difference can be explained by the fact that in our study group we included patients of both out of hospital cardiac arrest and in hospital cadiac arrest patients due to arrhythmias and all other causes like cardiogenic shock, hypoxia and s**e**ptic shock where as both the Bernard and HACA groups had included patients who suffered out of hospital cardiac arrest due to ventricular fibrillation. A large number of trials have documented the effectiveness of hypothermia in post CPR survivors of out of hospital cardiac a due to ventricular fibrillation. **This explains the overall low survival rate in our study as compared to the abovementioned studies. Further the limitation of this study is that it was conducted on less number of patients as it was a pilot study in our hospital.**The death rate in our study was 40 % at the time of discharge while 20 % patients went discharge against medical advice.This death rate was comparable to that seen in the casecontrol trial done by Bernard et al in multiple centres of Australia. In the Australian study the mortality rate was 51% the hypothermia group as compared to 68% in the normothermia group.

We further tried to look at the neurological outcome of patients who received**hypothermia post cardiac arrest at 48 hours and discharge of these patients.** It was assessed in terms of FOUR score, modified rankin scale and cerebral performance category scale.We observed that the mean FOUR score, mRS score and CPC scale at baseline were 3±1.26, 5±0 and 4.05±0.22 while at outcome were 5.1±5.75, 4.9±1.07 and 3.95±1.1. There was a trend towards improvement in FOUR score, mRS score and CPC scale from the baseline after the application of hypothermia.We further analysed the components of FOUR score at the outcome. We found that in the patients who got discharged, mean values of respiratory pattern and brainstem reflexes had shown maximum improvement at outcome as

compared to the eye and motor response in the patients who got discharged. This is in concordance with the study by E.AlThenayan[55] which suggests that absence of brainstem reflexes at day 3 is associated with poor neurological recovery. However, the overall improvement in mRS score was less as mRS does not include brainstem reflexes and is mainly affected by motor activity. The long term and short term neurological recovery was also seen in the HACA and Bernard study.In the HACA study group, favourable neurological recovery at the time of discharge was seen in 53% of the patients in hypothermia group as compared to 36% in the normothermia group. Similarly, 49% of the patients in hypothermia group had a favourable neurological recovery at the time of discharge as compared to 26% in normothermia group in the Bernard study. HACA study also looked at the looked favourable neurological recovery long term at 6 months follow up period and found that favourable neurological recovery in 52% the patients in the hypothermia group as compared to the 36% of the patients in the normothermia group. Thus, these trials showed that therapeutic hypothermia improve short-term neurological recovery in the post CPR survivors and the benefit was independent of the method used to induce hypothermia.At last, some more future long term research programs are needed to look for the longterm neurological outcome of post CPR patients. Although the major trials have shown the beneficial effects of hypothermia in the out of hospital cardiac arrest survivors due to ventricular fibrillation, there are recommendations which have quoted that hypothermia should be given to in hospital survivors also [96].The latest AHA guidelines recommended that comatose adult patients with ROSC after cardiac arrest **should undergo therapeutic hypothermia** for VF/pVT out of hospital cardiac arrest; non-VF/pVT (i.e., “non-shockable”) **and in-hospital cardiac arrest**. Thus, these guidelines have mentioned that hypothermia should be given to all cardiac arrest survivors irrespective of the cause of arrest and place of arrest**.**We divided the patients of our study into two groups: group 1- out of hospital cardiac arrest survivors(45% ie 9/20), group 2: in hospital cardiac arrest survivors(55% ie11/20). We

observed that the most common cause of arrest in our study was arrhythmias in group 1 **seen** in 77.8% patients as compared to group 2 (18.2%) with **a significantp value of 0.007**. We observed that the patients in group 1 mainly presented to us with the complains of breathlessness and unresponsiveness. Another important observation was that patients in group 1had a survival rate of 55.6% (5/9) as compared to group 2 where the survival rate was 27.3% (3/11). There is a considerable difference in the survival rates of two groups. This is in concordance with the major trials of hypothermia which have documented the beneficial effects of hypothermia in the out of hospital cardiac arrest survivors due to ventricular fibrillation. Since in our study, the majority of the patients of group 1 i.e. out of hospital cardiac arrest survivors had arrhythmias as the cause of arrest, there was a relatively better outcome in terms of survival in the patients of group1.

In our study, we found that the death rate was 44.4% and 72.7% in group 1 and 2 respectively. The number of patients who survived was higher in group 1(55.6%) as compared to group 2(27.3%). The difference in the survival rate of two groups can be explained by the fact that patients og group 2 (in hospital survivors) were having a baseline morbid condition and were sicker as compared to group1 who presented with cardiac arrest mainly due to arrhythmias as the major cause. We also compared the neurological outcomes of two groups. There was a trend towards improvement of FOUR score, CPC and mRS scale in patients of group 1 (out of hospital cardiac arrest survivors) vs group 2 (in hospital cardiac arrest). The mean values of FOUR score, mRS score and CPC scale at baseline and outcome in patients of group 1were 3.67±0.87 and 6.89±5.75; 4±0 and3.4±1.13;5±0and4.44±1.13 respectively while in group 2, the mean values at baseline and outcome were 2.45±1.29and 3.64±5..57; 4.09±0.3 and 4.36±0.92; 5±0 and 5.27±0.9 respectively.Hence , in our study we observed that therapeutic hypothermia helps improve the neurological recovery especially in patients who suffered out of hospital cardiac arrest due to arrhythmias.

Although therapeutic induced mild hypothermia has been effective and feasible in most studies, there are some complications associated with it. Soleimanpour H et al[97] published a review article on the main complications of mild Induced hypothermia after Cardiac Arrest. According to him,thereare many complications which do not require immediate treatment like the sinus bradycardia. Serious arrhythmias occur rarely when the temperature is above 30 degree centigrade. These generally start with atrial fibrillation and ultimately, they turn into ventricular fibrillation or ventricular tachycardia. However, insulin resistance and decreased insulin secretion leading to high blood sugar levels need immediate attention in the form of insulin infusion as increased blood glucose levels have detrimental effects on the neurological outcome and predisposes to sepsis. During the maintenance phase, the risk of occurrence of electrolyte abnormalities decrease. Electrolyte abnormalities occur in the form of hypokalemia, hypophosphatemia and magnesium deficiency. These are common during the induction phase due to the increased renal excretion due to changes in the cardiac preload, blood circulation and tubular function . However, at the same time, the risk of pneumonia, sepsis, wound infections and bed sores increase during the maintenance phase. The rewarming phase is marked by electrolyte shift from the intracellular to the extracellular compartment, thus, it may lead to hyperkalemia. In our study group, we observed that the most common complications were sepsis, arrhythmias,hyperglycemia and hypokalemia. 70% of patients who underwent hypothermia landed up with sepsis,65% of the patients had arrhythmias, hyperglycemia was reported in 65% of the patients and another 50% suffered from hypokalemia during the induction process. Hyperkalemia was seen in 20% of the patients while hypocalcemia and hypomagnesemia was seen in 5% of the patients. Amongst these complications: hypokalemia, hypocalcemia and hypomagnesemia were most commonly observed during the induction phase. This is consistent with the literature where electrolyte imbalance are most commonly seen during the induction phase. Although hypothermia is associated with complications yet it has been approved

as an effective therapeutic treatment for post CPR patients as it leads to considerable reduction in mortality and improved neurological function in these patients. Moreover, the complications associated are more or less correctable and can be effectively managed if carefully monitored and looked for in the intensive care setting. Hence therapeutic induced moderate hypothermia helps in the survival and improvement of neurological functions of post cardiac arrest patients.

SUMMARY AND CONCLUSION

A total of 28 patients were screen to be included in the study. Out of these 28 patients,8 patients went discharge against medical advice before completing the hypothermia protocol**.**Thus the final study cohort consisted of 20 patients.The mean age of the patients was64.4±11 years. In our study cohort, 70% of patients were males and 30% of patients were females. We observed that 45% the patients had arrest at home(group1) while the rest 55% suffered from cardiac arrest within the hospital (group 2).The patients had presented to the hospital with the following complaints: breathlessness, cough, chest pain, headache, unresponsiveness and vomitings. Amongst these, the leading presenting complaints were breathlessness and unresponsiveness in group 1 patients. It was observed that in 55% of the patients who belonged to group 1,CPR was initiated within 3 minutes of cardiac arrest,in 30% of the patients it was initiated after 8 to 10 minutes of cardiac arrest while in the rest 15% of the patients it was started within 4 to 7 minutes of cardiac arrest.The most common complications associated with hypothermia were sepsis, arrhythmias hyperglycemia and hypokalemia. 70% of patients who underwent hypothermia landed up with sepsis, 65% of the patients had arrhythmias, hyperglycemia was reported in 65% of the patients and another 50% suffered from hypokalemia during the induction process. Hyperkalemia,hypocalcemia and hypomagnesemia was seen in 20%, 5% and 5% of the patients respectively. Majority of the electrolyte disturbances occur during the Induction phase. During the maintenance phase the major complications were arrhythmias and sepsis to the tune of 92.3 percent and 57.1% respectively. During the rewarming phase, the main complication was hyperkalemia.

The outcomes of the patients who underwent hypothermia post cardiopulmonary resuscitation were as follows: 40% of the patients got discharged, 40% died while the rest 20% went discharge against medical advice. The family members of the 4 patients who had gone

discharge against medical advice after completion of hypothermia protocol were contacted telephonically and we found that all these 4 patients could not survive on their way to home. We studied the neurological outcomes as per the improvement in three scales: four score, mRS scale and cerebral performance category scale. We observed that the mean FOUR score at baseline was 3 while at outcome it was 5.1. There was a trend towards improvement from the baseline post application of hypothermia although the value is non significant (p value=0.086). The mean mRS at baseline and outcome was 5±0 and 4.9±1.07 while the mean CPC values at baseline and outcome was 4.05±0.22 and 3.95±1.1 respectively. We compared the survival rates and neurological outcomes in group 1 and 2.The number of patients who survived was higher in group 1(55.6%) as compared to group 2(27.3%). We also compared the neurological outcomes of two groups. There was a trend towards improvement of FOUR score, CPC and mRS scale in patients of group 1 (out of hospital cardiac arrest survivors) vs group 2 (in hospital cardiac arrest). The mean values of FOUR score, mRS score and CPC scale at baseline and outcome in patients of group 1were 3.67±0.87 and 6.89±5.75; 4±0 and3.4±1.13;5±0and4.44±1.13 respectively while in group 2, the mean values at baseline and outcome were 2.45±1.29and 3.64±5..57; 4.09±0.3 and 4.36±0.92; 5±0 and 5.27±0.9 respectively. Hence , in our study we observed that therapeutic hypothermia helps improve the neurological recovery especially in patients who suffered out of hospital cardiac arrest.

Limitations

The number of patients was small as it was a pilot study in our institute.
There was no comparable control group.
This study did not look at the long term neurological outcome of these patients.

Conclusions

Therapeutic hypothermia is a potential treatment for post cardiac arrest survivors. Although it is associated with many complications, most of these are correctable and can be meticulously handled if these are carefully monitored in the intensive care setting. It not only helps improve survival of post cardiac arrest patients but also helps in the neurological outcome Among the components of FOUR score, brainstem reflexes and respiratory pattern are the components which show maximum improvement. We found that patients of group 1 (out of hospital cardiac arrest) patients had a better survival rate and a significant trend towards improvement in the FOUR score, mRS score and cerebral performance category scale as compared to group 2 (in hospital cardiac arrest) patients. This reinforces that hypothermia should be given to all post cardiac arrest survivors especially in the patients who suffer cardiac arrest in the out of hospital setting.

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SERIAL NO	NAME	AGE (years)	GENDER	REASON FOR ADMISSION	PRIMARY DIAGNOSIS	DM	HTN	CAD	Neuro	CAUSE OF ARREST	TIME OF ARREST	TIME OF INITIATION OF CPR	ROSC TIME	TIME OF ARREST- TIME OF INITIATION OF CPR	TIME OF ARREST- ROSC TIME	TIME OF INITIATION OF CPR- ROSC TIME	PLACE OF ARREST		OUTCOME
1	MA	57	Female	Unresponsiveness	DM/HTN/CAD	Y	Y	Y	-	Arrythmias	12:30	12:38	12:50	8	20	12	Home	1	Died
2	NS	70	Male	chest pain	DM/HTN/ACS/LVF	Y	Y	Y	-	Arrythmias	18:50	18:50	19:10	0	20	20	Hospital	2	DAMA
3	GS	75	Male	chest pain	DM/HTN/ACS/LVF	Y	Y	Y	-	Arrythmias	09:07	09:08	09:13	1	6	5	Hospital	2	Died
4	SM	68	Female	Unresponsiveness	DM/Swine Flu	Y	-	-	-	Arrythmias	16:50	17:00	17:15	10	25	15	Home	1	Discharge
5	DG	67	Male	Headache,vomittimg	Right frontal ICH/IVH/SAH	-	-	-	y	Hypoxia	10:05	10:05	10:15	0	10	10	Hospital	2	Died
6	NS	63	Male	Unresponsiveness	DM/HTN/Hypothroid/ACS/Arrythmias	Y	Y	Y	-	Cardiogenic shock	11:00	11:00	11:20	0	20	20	Hospital	2	Discharge
7	PK	57	Female	chest pain	DM/Hypothyroid/AWMI/Arrythmias	Y	-	Y	-	Hypoxia	06:30	06:30	06:45	0	15	15	Hospital	2	Died
9	DJ	63	Male	Unresponsiveness	DM/HTN/Post CABG/ICMP/AWMI/Arrythmias	Y	Y	Y	-	Arrythmias	20:00	20:10	20:25	10	25	15	Home	1	DAMA
10	NJ	67	Female	Unresponsiveness	OSA/RF type 2/LV dysfunction (EF - 40%)/VT	-	-	Y	-	Arrythmias	01:15	01:22	01:38	7	23	16	Home	1	DAMA
11	V	55	Male	Unresponsiveness	Post liver transplant/ LV dysfunction	-	-	Y	-	Arrythmias	03:20	03:28	03:45	8	25	17	Home	1	Discharge
13	SD	80	Female	Breathlessness	DM/HTN/CAD/ACS/LV dysfunction (EF - 30%)	Y	Y	Y	-	Cardiogenic shock	12:20	12:30	12:40	10	20	10	Home	1	Discharge
14	HS	52	Male	Breathlessness	CVA/CAD/AWMI	-	-	Y	y	Cardiogenic shock	11:25	11:25	11:35	0	10	10	Hospital	2	Died
15	MR	52	Male	Breathlessness	DM/COPD/LV dusfunction (EF - 20%)	Y	-	Y	-	Cardiogenic shock	08:55	08:55	09:03	0	8	8	Hospital	2	DAMA
16	RR	67	Male	Breathlessness	DM/HTN/ACS	Y	Y	Y	-	septic shock	13:00	13:00	13:03	0	3	3	Hospital	2	Died
17	PS	77	Male	Breathlessness	OSA/HTN/Morbid Obesity/Hypothyroid	-	Y	-	-	Hypoxia	10:35	10:42	11:09	7	30	27	Home	1	Died
18	PK	73	Female	Unresponsiveness	Post TKR/Carcinoma breast/AWMI	-	-	Y	-	Cardiogenic shock	15:40	15:41	15:46	1	6	5	Hospital	2	Discharge
19	GS	65	Male	Unresponsiveness	HTN/Post Cholecystectomy/LV dysfunction(EF - 18%)	-	Y	Y	-	arrythmias	13:30	13:38	13:48	8	18	10	Home	1	Discharge
20	HS	86	Male	Unresponsiveness	DM/HTN/BPH/IHD	Y	Y	Y	-	Arrythmias	22:50	22:56	23:10	6	20	14	Home	1	Discharge
21	GS	41	Male	Breathlessness	Pulmonary thromboembolism/RV strain	-	-	-	-	Cardiogenic shock	13:06	13:06	13:12	0	6	6	Hospital	2	Died
22	AG	53	Male	Headache, Vomiting	DM/HTN/CKD/SDH	Y	Y	-	y	Hypoxia	13:54	13:54	14:24	0	30	30	Hospital	2	Discharge

SERIAL NO	NAME	Hospital stay	Eye response Baseline	Motor response Baseline	Brainsteam reflexs Baseline	Respiration Baseline	FOUR SCORE Baseline	FOUR SCORE 48hours	Eye response_ Outcome	Motor response_ Outcome	Brainsteam reflexs Outcome	Respiration Outcome	FOUR SCORE Outcome	FOUR SCORE _	MRS_ Baseline	MRS 48hours	MRS_Outcome	MRS_	CPC_Baseline	CPC 48hours	CPC_Outcome	CPC_	Hyperkalemia Phase
1	MA	4	0	1	2	1	4	3	0	0	0	0	0	w	5	5	6	w	4	4	5	w	-
2	NS	3	0	0	0	0	0	0	0	0	0	0	0	n	5	5	5	N	5	5	5	N	-
3	GS	3	0	0	1	1	2	2	0	0	0	0	0	w	5	5	6	w	4	4	5	w	-
4	SM	24	1	1	1	1	4	6	1	1	4	4	10	i	5	5	3	I	4	4	2	I	-
5	DG	2	0	0	1	0	1	1	0	0	0	0	0	w	5	5	6	w	4	4	5	w	-
6	NS	32	0	0	2	1	3	8	2	2	4	4	12	i	5	5	4	I	4	4	3	I	-
7	PK	6	0	1	1	1	3	2	0	0	0	0	0	w	5	5	6	w	4	4	5	w	Rewarming
9	DJ	3	0	0	1	1	2	2	0	0	1	1	2	n	5	5	5	N	4	4	4	N	-
10	NJ	4	0	1	2	1	4	2	0	0	1	1	2	w	5	5	5	N	4	4	4	N	-
11	V	17	1	1	1	1	4	9	1	1	4	4	10	i	5	5	3	I	4	4	2	I	-
13	SD	24	1	1	1	1	4	8	3	1	4	4	12	i	5	5	4	I	4	4	3	I	-
14	HS	4	0	0	1	2	3	3	0	0	0	0	0	w	5	5	6	w	4	4	5	w	-
15	MR	6	0	1	2	1	4	4	1	1	1	1	4	n	5	5	5	N	4	4	4	N	-
16	RR	3	0	0	1	0	1	1	0	0	0	0	0	w	5	5	6	w	4	4	5	w	-
17	PS	7	0	0	2	1	3	3	0	0	0	0	0	w	5	5	6	w	4	4	5	w	-
18	PK	16	0	1	2	1	4	10	3	3	4	4	14	i	5	5	4	I	4	4	3	I	Rewarming
19	GS	7	0	1	2	2	5	9	3	1	4	4	12	i	5	5	4	I	4	4	3	I	-
20	HS	45	0	0	1	2	3	7	3	3	4	4	14	i	5	5	4	I	4	4	3	I	-
21	GS	2	0	0	2	1	3	2	0	0	0	0	0	w	5	5	6	w	4	4	5	w	Rewarming
22	AG	27	0	1	1	1	3	7	1	1	4	4	10	i	5	5	4	I	4	4	3	I	Rewarming

SERIAL NO	NAME	Hyperkalemia Step Taken	Hypokalemia Phase	Hypokalemia Step Taken	Hypocalcemia Phase	Hypocalcemia Step Taken	Hypomagnesemia Phase	Hypomagnesemia Step Taken	Hyperglycemia Phase	Hyperglycemia Step Taken	Arrythmias Phase	Arrythmias_Step Taken	Sepsis Phase	Sepsis_Step Taken	Hypotension Phase	Hypotension Step Taken
1	MA	-	induction	kcl	-	-	-	-	-	-	sinus brady,(m)	none	Maintainance	Antibiotic	-	-
2	NS	-	induction	kcl	-	-	-	-	Maintainance	Insulin infusion	sinus brady,(m)	ECG monitoring	-	-	-	-
3	GS	-	-	-	Maintainance	i/v calcium	-	-	-	-	AF(m)	cardioversion	Maintainance	Antibiotic	-	-
4	SM	-	Maintainance	kcl	-	-	-	-	Maintainance	Insulin infusion	-	-	-	-	Induction	ionotropes
5	DG	-	Maintainance	kcl	-	-	-	-	Maintainance	Insulin infusion	-	-	Maintainance	Antibiotic	Maintainance	ionotropes
6	NS	-	-	-	-	-	-	-	ewarMaintainancein	Insulin infusion	sinus brady,(m)	ECG monitoring	Maintainance	Antibiotic	Maintainance	ionotropes
7	PK	antihyperkalemia	-	-	-	-	-	-	Maintainance	Insulin infusion	sinus brady,(m)	ECG monitoring	Induction	Antibiotic	-	-
9	DJ	-	induction	kcl	-	-	-	-	Induction	Insulin infusion	-	-	Induction	Antibiotic	Induction	Inotropes
10	NJ	-	Maintainance	kcl	-	-	-	-	Maintainance	Insulin infusion	sinus brady,(m)	ECG monitoring	-	-	-	-
11	V	-	-	-	-	-	-	-	Maintainance	Insulin infusion	VF(m)	cardioversion	Maintainance	Antibiotic	Induction	ionotropes
13	SD	-	-	-	-	-	-	-	Maintainance	Insulin infusion	-	-	Maintainance	Antibiotic	Induction	ionotropes
14	HS	-	induction	kcl	-	-	-	-	-	-	sinus brady,(m)	ECG monitoring	Induction	Antibiotic	-	-
15	MR	-	induction	kcl	-	-	-	-	Induction	Insulin infusion	-	-	ewarMaintainancei	Antibiotic	-	-
16	RR	-	induction	kcl	-	-	-	-	-	-	AF(m)	cardarone	Induction	Antibiotic	-	-
17	PS	-	-	-	-	-	-	-	Maintainance	Insulin infusion	AF(m)	cardarone	Maintainance	Antibiotic	-	-
18	PK	antihyperkalemia	-	-	-	-	-	-	-	-	sinus brady,(m)	ECG monitoring	-	-	-	-
19	GS	-	Maintainance	kcl	-	-	-	-	-	-	-	-	Maintainance	Antibiotic	Maintainance	ionotropes
20	HS	-	-	-	-	-	Maintainance	i/v mgso4	Maintainance	insulin infusion	AF(Induction)	cardioversion	-	-	-	-
21	GS	antihyperkalemia	-	-	-	-	-	-	-	-	-	-	Induction	Antibiotic	Maintainance	ionotropes
22	AG	antihyperkalemia	-	-	-	-	-	-	Maintainance	insulin infusion	AF(m)	cardarone	-	-	-	-

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The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.05.2019 has approved the plan of thesis of **Dr. Nitika Mahajan**, a student of your college for **DM Neurology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

Role of therapeutic hypothermia on neurological outcome in post cardiac arrest patients

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The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

SP Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

ROLE OF THERAPEUTIC HYPOTHERMIA ON NEUROLOGICAL OUTCOME IN POST CARDIAC ARREST PATIENTS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED
IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

in

Neurology

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

FEBRUARY, 2019

DR NITIKA MAHAJAN

DEPARTMENT OF NEUROLOGY
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ABSTRACT OF PLAN OF THESIS

Title	Role of therapeutic hypothermia on neurological outcome in post cardiac arrest patients
For the degree of	D.M.Neurology
Name of the candidate	Dr Nitika Mahajan
Supervisor	Dr. Rajinder Kumar Bansal, Professor, Department of Neurology, Dayanand Medical College and Hospital, Ludhiana
Co-supervisor	Dr. Gurpreet S Wander, Professor & Head, Department of Cardiology, DMCH, Ludhiana Dr. Birinder Singh Paul, Professor, Department of Neurology, Dayanand Medical College and Hospital, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Development of therapeautic hypothermia in post cardiac arrest survivors has been associated with decreased mortality and improved neurological outcomes. We shall conduct a prospective observational study to see its effect on neurological recovery of post cardiac arrest survivors in our hospital.

Aim of Study: Role of therapeutic hypothermia on neurological outcome in post cardiac arrest patients.

Materials & Methods: Detailed history and relevent data of all patients who will receive therapeutic hypothermia post cardiac arrest will be collected. The data will be analysed for neurological recovery and survival outcome in patients at the time of discharge from hospital.

Clinical Significance: To offer therapeutic hypothermia to post cardiac arrest comatose survivors would potentially have a major impact on clinical profile in terms of neurological recovery and mortality

Keywords: TH (Therapeautic hypothermia), CA (cardiac arrest)

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"ROLE OF THERAPEUTIC HYPOTHERMIA ON NEUROLOGICAL OUTCOME IN POST CARDIAC ARREST PATIENTS"** exist in the Department of Neurology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself under our supervision and guidance.

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APPROVAL PROFORMA
BY
RESEARCH & ETHICAL COMMITTEE
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1. HOD Pharmacology	1. HOD Physiology
2. HOD Surgery	2. HOD Pathology
3. HOD Pathology	3. HOD Pharmacology
4. HOD Medicine	4. HOD SPM
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Research Committee

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Research Committee

Approved: Yes / No

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Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Dr. Nitika Mahajan
2	NAME OF THE INSTITUTE	Dayanand Medical College, Ludhiana.
3	COURSE OF STUDY AND SUBJECT	D.M. Neurology
4	DATE OF ADMISSION OF COURSE	13th August 2018
5	TITLE OF THE TOPIC	Role of therapeutic hypothermia on neurological outcome in post cardiac arrest patients

6 BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Therapeutic hypothermia is defined as an intentional reduction of a patients' core temperature to 32°C–35°C. This is being used with increasing frequency as a method to prevent various types of neurologic injury.[1] Hence the issue of temperature control and temperature manipulation is gaining importance in neurocritical care. According to the most recent guidelines from the American Heart Association and the European Resuscitation Council it is recommended to induce hypothermia for selected patients who remain comatose following a witnessed cardiac arrest.[2] Therapeutic hypothermia is also used therapeutically in the treatment of severe traumatic brain injury, stroke, hepatic failure, spinal cord injury, myocardial infarction, and numerous others. Although the clinical trials of TH for head trauma and stroke have so far failed to confirm any benefit in human beings despite a vast preclinical literature. Therefore, it is now critical to understand the fundamental explanation for the success of TH in some, but not all, clinical trials. However the role of therapeutic hypothermia has been proven in patients of post cardiac arrest and in neonatal hypoxic ischemic encephalopathy. So we would like to study the effect of therapeutic hypothermia on neurological recovery of post cardiac arrest patients.

6.2 REVIEW OF LITERATURE

Cardiac arrest is often associated with widespread cerebral ischemia which frequently leads to severe neurologic impairment. Therapeutic hypothermia has been recommended for post cardiac arrest coma due to ventricular fibrillation.M. Holzer et al [3] studied whether mild systemic hypothermia increases the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation. They conducted a randomised study on 136 patients who had been successfully resuscitated after cardiac arrest. They thereby concluded that therapeutic mild hypothermia increased the rate of a favorable neurologic outcome and reduced mortality in patients who had received therapaeutic hypothermia. There is paucity of studies which have evaluated whether therapeutic hypothermia could be effectively implemented in intensive care practice and whether it would improve the outcome of all comatose patients with cardiac arrest, including those with shock or with cardiac arrest due to nonventricular fibrillation rhythms. Mauro Oddo et al [4] conducted a Retrospective study on109 comatose patients with out-of hospital cardiac arrest due to ventricular fibrillation and nonventricular fibrillation rhythms (asystole/pulseless electrical activity). They found that therapeutic hypothermia had a major positive impact on the outcome of patients with cardiac arrest due to ventricular fibrillation as compared to patients who had arrest due to non VF rhythms. Therapeutic hypothermia was of particular benefit in patients with short duration of cardiac arrest (<30 minutes). They concluded that Therapeutic hypothermia for the treatment of post cardiac arrest coma can be successfully implemented in intensive care practice with a major benefit on patient outcome, which appeared to be related to the type

and the duration of initial cardiac arrest. Therapeutic hypothermia has been associated with various adverse effects like arrhythmias, electrolyte imbalance and predisposition to infections. Various studies have shown that it is feasible and not associated with case fatalities. Jasmin Arrich, [5] conducted a study on the clinical application of mild therapeutic hypothermia after cardiac arrest on 650 patients. Of all hypothermia patients, 15 (3%) had an episode of hemorrhage and 28 patients (6%) had at least one episode of arrhythmia within 7 days after cooling. There were no fatalities as a result of cooling. They concluded that therapeutic hypothermia is feasible and can be used safely and effectively outside a randomized clinical trial. The role of therapeutic hypothermia is being studied in post trauma and stroke patients. Most studies have failed to show benefit in these patients. However the role has been well established in post cardiac arrest survivors .Michael Holzer, MD et al [6] meta-analysis which included randomized and quasi-randomized, controlled trials of adults who were successfully resuscitated, where therapeutic hypothermia was applied within 6 hrs after arrival at the emergency department and where the neurologic outcome was compared. They concluded that mild therapeutic hypothermia improves short term neurologic recovery and survival in patients resuscitated from cardiac arrest of presumed cardiac origin. Its long-term effectiveness and feasibility at an organizational level need further research. Birger Wolff et al [7] conducted a study to evaluate the effect of early achievement of mild therapeutic hypothermia on the neurologic outcome after cardiac arrest. Forty-nine consecutive patients successfully resuscitated from cardiac arrest were enrolled. They concluded that early achievement of mild Therapeutic

hypothermia by endovascular cooling appears to reduce hypoxic brain injury and to favour a good neurologic outcome after cardiac arrest. Various studies have been conducted for prognostication of patients of poat cardiac arrest.

Andrea O et al [8] performed a prospective study named Prognostication after Cardiac Arrest and Hypothermia prospective study to verify the prognostic value of clinical and electrophysiological variables in the TH setting .A total of 111 consecutive comatose survivors of CA treated with TH were prospectively studied over a 3-year period. Neurological examination, electroencephalography (EEG), and somatosensory evoked potentials (SSEP) were performed immediately after TH, at normothermia and off sedation. Neurological recovery was assessed at 3 to 6 months, using Cerebral Performance Categories (CPC).The presence of at least 2 independent predictors out of 4 (incomplete brainstem reflexes, myoclonus, unreactive EEG and absent cortical SSEP) accurately predicted poor long-term neurological recovery. EEG reactivity significantly improved the prognostication. TH may modify outcome prediction after cardiac arrest, implying that some clinical features should be interpreted with more caution in this setting as compared with the AAN guidelines. EEG background reactivity is useful in determining the prognosis after cardiac arrest treated with TH.

E. Al Thenayan, et al [9] performed a study was to reassess the validity of the various predictors in post-CA patients treated with TIMH. Retrospective chart review of 37 consecutive adults who were comatose after resuscitation from CA and treated with TIMH. They showed that none of six patients without pupillary reactivity, six without corneal reflexes on day 3, or eight with myoclonus status epilepticus recovered awareness. Two of 14 patients with

motor responses no better than extension at day 3 recovered motor responses only after 6 days post arrest (one at 5 and one at 6 days post-rewarming) and regained awareness. They concluded that Loss of motor responses better than extension on day 3 was not prognostically reliable after therapeutic induced mild hypothermia for comatose cardiac arrest survivors. None of the patients who lost pupillary or corneal reflexes on day 3 or developed myoclonus status epilepticus recovered awareness. Ka Wai Cheung et al [10] made a systematic review of randomized controlled trials of therapeutic hypothermia as a neuroprotectant in post cardiac arrest patients. They studied whether induced hypothermia improves neurologic outcome, decreases mortality, or is associated with an increased incidence of adverse events. Pooled data demonstrated that mild hypothermia decreased in hospital mortality (relative ratio [RR] 0.75; 95% confidence interval [CI], 0.62–0.92) and reduced the incidence of poor neurologic outcome (RR 0.74; 95% CI, 0.62–0.84). They concluded that therapeutically induced mild hypothermia decreases in-hospital mortality and improves neurologic outcome in comatose cardiac arrest survivors. The possibility of treatment-limiting side effects cannot be excluded.

Therapeutic Hypothermia (TH) has been shown to improve neurological recovery and reduces mortality after global ischemia, such as in patients with cardiac arrest [11-13], and also in infants with moderate or severe hypoxic-ischemic encephalopathy.[14] The therapeutic implications of hypothermia reentered the modern literature starting in the 1940-50s with the specific use of TH in cardiac arrest patients [15] in 1959. Thus we would like to

elucidate its role on neurological recovery in our hospital on postcardiac arrest patients.

6.3 AIMS AND OBJECTIVES OF THE STUDY

To study the effect of therapeutic hypothermia on neurological outcome in post cardiac arrest patients.

7.0 MATERIALS AND METHODS

7.1 SOURCE OF DATA

We shall conduct a prospective observational study on a total of 20 patients. Those patients who are cardiac arrest survivors and remain comatose post CPR would be enrolled in our study. Hypothermia will be created using a special blanket/mattress and protocol will be followed to prevent shivering.

7.2 METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA

1. Cardiopulmonary Resuscitation (CPR) initiated within 10 minutes of cardiac arrest.
2. Return of spontaneous circulation within 30 minutes of recognition of the cardiac arrest; MAP ≥ 60 for at least 30 minutes post ROSC with or without vasoactive medication.
3. Initiation of Induced Hypothermia within 6 hours of collapse.
4. Initial body temperature must be greater than 30°C.
5. No purposeful movement to command and Glasgow Coma Scale < 6.
6. Age > 18
7. Female < 50 years must have negative urine HCG

EXCLUSION CRITERIA

1. Prolonged arrest time longer than 60 minutes or down time without BLS longer than 10 minutes
2. Age less than 18 years, Pregnancy, Uncontrolled bleeding, thrombocytopenia or other coagulopathy
3. DNR or DNI status

4. Refractory arrhythmias
5. Hypoxemia with Saturation < 85% for more than 15 minutes

An informed consent will be taken from the attendants of the patient. Hypothermia would be induced using a special blanket/mattress and an anti shivering protocol would be followed to prevent shivering.

Procedure: The provision of therapeutic hypothermia to survivors of cardiac arrest consists of three phases: Induction, Maintenance and Rewarming.

Induction -It would be done using a hypothermia blanlet/ mattress

Maintenance with Cooling Blanket Machine

1. Maintain patient temperature at 33° C for 24 hours from initiation of cooling.
2. Management of shivering, hypotension (MAP<80mm Hg), dysarrythmias, electrolyte disturbances to be done.
3. Be alert for early signs of shivering and initiate shivering protocol

Analgesia/Sedation and Shivering

Propofol or Dexmedetomidine will be utilized shivering prevention. Buspirone, Acetaminophen, Midazolam, and Neuromuscular Blocking Agents (NMBA) will be administered on an as needed basis to prevent shivering

Electrolyte Replacement

1. Check STAT potassium and magnesium for any cardiac dysrhythmia and every 4 hours

2. After any replacement, check electrolyte level 1 hr after completion of replacement.

3. During cooling phase: replace K+ < 3.5

replace Mg++ < 2.0

replace ionized Ca++ < 1.0

serum Ca++ < 7.5

4. Discontinue K replacements 8 hours prior to rewarming
5. Discontinue Mg and Ca replacements once warming has begun

Rewarming

1. The rewarming process should be gradual and take place ideally over 12 or more hours.
2. Target is 37° C over approximately 12 hours at a rewarming rate of 0.33° C/hour
3. Monitor for hyperthermia, hypotension and hyperkalemia
4. May discontinue paralytics when temperature is 36° C
5. Once a temperature of 37° C is reached, leave a cooling blanket on top of the patient with machine set to 37° C for the remainder of the 48hr period of therapy to avoid rebound hyperthermia

Outcome

Primary outcome was to study the effect of therapeutic hypothermia on the neurological outcome which is assessed by doing neurological examination (four score) and using mRS scale and CPC scale after 48 hours of therapeutic hypothermia and at the time of discharge or 7 days. Secondary outcome would be to see the effect of therapeutic hypothermia on mortality.

Modified Rankin Scale	Criteria
0 - No Symptoms	No residual symptoms from injury.
1 - No Significant Disability	Able to carry out all usual activities, despite some symptoms
2 - Slight Disability	Able to look after own affairs without assistance from another person, but unable to carry out all previous activities
3 - Moderate Disability	Requires some help, but able to walk without assistance from another person
4 - Moderately Severe Disability	Unable to attend to own bodily needs and unable to walk without assistance from another person
5 - Severe Disability	Requires constant nursing care and attention, bedridden, incontinent
6 – Dead†	Died as a result of traumatic incident

STATISTICAL ANALYSIS

The results would be analysed using appropriate statistical methods

7.3 **DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.**

Yes, investigations like-

CBC

Electrolytes

Calcium

Magnesium

PTI/PTTK

ECG

Blood sugar

ABG analysis

INTERVENTION

Therapeutic hypothermia would be induced using cooling blanket/mattress as per the protocol discussed above

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached Herewith

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14. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxicischemic encephalopathy. The New England journal of medicine. 2005;353:1574–84.
15. Benson DW, Williams GR, Spencer FC, Yates AJ. The use of hypothermia after cardiac arrest. Anesthesia and analgesia. 1959;38:423–8.

PROFORMA

Sr. No:-

- Name MRD number-
- Age
- gender
- Occupation
- Address
- Phone number
- Reason for admission

- Primary diagnosis

- Time of arrest
- Time of initiation of CPR
- Return of spontaneouscirculation time(ROSC time)
- Ionotropic support
- Mean arterial pressure
- Cause of arrest
- Place of cardiac arrest- hospital or home

Signature of Candidate **Signature of Supervisor**

Vitals	Heart rate	Blood presssure	Temperature	Pupil charting
Induction Beginning completion				
Maintainance Beginning completion				
Rewarming Beginning completion				

Neurological examination

Vital monitoring

Vitals	Heart rate	Blood presssure	Temperature
Induction Beginning completion			
Maintainance Beginning completion			
Rewarming Beginning completion			

Monitoring clinical improvement

Four score assessment scale

- Baseline score
- After completion of hypothermia
- At 7 days/ discharge

Signature of Candidate

Signature of Supervisor

Scales	Hypothermia initiation	48 hours	Discharge
MRS scales			
CPC scale			

LABS

INVESTIGATIONS	Baseline	Induction phase	Maintenance phase	Rewarming phase
Potassium				
Calcium				
Magnesium				
CBC				
PTI				
PTTK				
ECG				
ABG				

Complication	**during which phase**	**Steps taken**
Hypo/hyperklemia		
hypocalcemia		
hypomagnesemia		
hyperglycemia		
arrythmias		
sepsis		
hypotension		
others		

Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

.....am willing to participate in the study **"Role of therapeutic hypothermia on neurological outcome in post cardiac arrest patients"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य "**Role of therapeutic hypothermia on neurological outcome in post cardiac arrest patients**" में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"Role of therapeutic hypothermia on neurological outcome in post cardiac arrest patients" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ